

STELLENBOSCH UNIVERSITY

**The contextual quality of life of women with cervical cancer in the Western
Cape, South Africa.**

George Campbell du Toit

MB ChB; MMed (O & G); FCOG (SA); Cert Gynae Oncol (HPCSA); FRANZCOG



Doctor of Philosophy at Stellenbosch University

UNIVERSITEIT
STELLENBOSCH
UNIVERSITY
Department of Obstetrics and Gynaecology
Faculty of Medicine and Health Sciences



Promoter: Prof. T.F. Kruger

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Declaration

I, George Campbell du Toit, hereby declare that the work contained in this dissertation is my own original work and that I have not previously, in its entirety or in part, submitted it at any university for a degree.

Date: December 2018

**This work is dedicated to my beloved wife, Marlène
and our children, Odette and Paul-Jacob.**

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Aan God, my skepper: “Ek sal die Here loof wat my tot die regte insig gebring het; selfs in die nag bly ek bewus van wat Hy my leer.” *Psalms16:7*

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Abstract of thesis

Chapter 1

The chapter describes the first phase of the research, which to identify an appropriate questionnaire to assess the quality of life (QOL) of South African women with cervical cancer. The literature on QOL assessment, with its role in oncology research practice, is reviewed. Additionally, the theory underlining the development of oncology-related questionnaires is discussed. This is followed by reviewing the theory of translation of questionnaires into target population languages. Furthermore, factors that are important in deciding on an appropriate questionnaire are discussed. A systemic review of cervical cancer QOL studies is conducted, which identifies the European Organisation for Research and Treatment of Cancer (EORTC) QLQ C30 and CX24 as appropriate questionnaires for South African women with cervical cancer. Three published articles (first author GC du Toit) describing the selection of EORTC QLQ C30, the translation, validation and psychometric analysis of the translated versions of EORTC QLQ C24 questionnaires conclude the chapter. The EORTC has been given official recognition and certification by the Xhosa and Afrikaans translated versions of EORTC QLQ CX24.

Chapter 2

The chapter reviews the literature of the medical contextual factors influencing the QOL of women with cervical cancer. The specific factors discussed are a) age at diagnosis b) stage of disease c) treatment and d) comorbidities including Acquired Immune Deficiency Syndrome (AIDS). Moreover, the interaction between these factors and the incidence of cervical cancer are analyzed. Furthermore, the review highlights the disparity between objectively documented medical complications of treatment and the patient's reported QOL.

Chapter 3

A literature review of non-medical contextual factors influencing the QOL of women with cervical cancer is presented in this chapter. These contextual factors include race, socioeconomic factors, and educational factors. Also, the interplay between these factors and the incidence of cervical cancer is analyzed.

Chapter 4

Original research is presented in this chapter as a prospective study of the QOL of women treated for cervical cancer. The influence of medical and contextual factors on the various QOL domains are analyzed. The difference in the QOL between women receiving radiation therapy versus chemo-radiation therapy identifies the differential effect the two modalities have on the specific QOL items, e.g. pain. The chapter is presented as a publication (first author GC du Toit).

Chapter 5

Original research is presented of a cross-sectional study describing the influence of contextual factors on the QOL of Human Immunodeficiency Virus (HIV)-positive women with *newly diagnosed* cervical cancer. A second study is presented as an original research, describing a prospective study of demographic features and QOL of HIV-positive women with cervical cancer undergoing treatment. Subsequently, the differences in HIV-positive and HIV-negative women's demographics and QOL prior and subsequent to treatment are described. The chapter is presented in two publications (first author GC du Toit).

Chapter 6

The chapter presents an original research as a cross-sectional study of the contextual QOL of cervical cancer survivors, 18 months after the completion of therapy. The effect of the various medical and contextual factors on QOL are analyzed.

Chapter 7

A literature review of qualitative research and cervical cancer is presented. The theory and methods involved in qualitative research are described. A literature review of women's qualitative experience, with regards to the various aspects of cervical cancer, is presented. The aspects covered include primary prevention and secondary prevention as represented by *human papillomavirus* (HPV) vaccine and cytology. Women's experience with the diagnosis, treatment, and sequelae of cervical cancer are discussed as the tertiary aspects. The chapter illustrates the contrasts and similarities between the qualitative and quantitative QOL research.

Chapter 8

The life experience of women with cervical cancer is presented as an original research of an explorative quantitative study. This research uses thematic analysis of women's own narrative of their experience. The women's experience is analyzed using the Kübler-Ross model. Additionally, the psychological phenomena related to the reaction of stress, based on the defense and coping mechanisms, are discussed. The analysis highlights the dichotomy of coping and defense mechanisms in these women.

Chapter 9

The dissertation concludes that QOL analysis should be a part of clinical practice. Women with advanced cervical cancer have a guarded prognosis. The influence of their personal contextual factors should be considered to be a part of decisions made during therapy. HIV-positive status does not preclude specific treatment modalities but it should be judiciously used, not to compromise the QOL. Appropriate psychological support and care should be given to women with cervical cancer.

Opsomming van tesis

Hoofstuk 1

Die hoofstuk beskryf die eerste fase van die navorsing waartydens 'n geskikte vraeboog vir die evaluering van lewenskwaliteit van Suid Afrikaanse vroue met servikskanker geïdentifiseer word. 'n Literatuuroorsig oor lewenskwaliteit evaluering se rol tydens onkologiese navorsing praktyk word bespreek. Dit bied 'n oorsig van die agtergrond en ook die teorie van die ontwikkeling van vraeboë. 'n Oorsig van vertalings teorie na teken taalgroepe van vraeboë volg. Faktore wat 'n rol speel in die identifisering van 'n geskikte vraeboog word bespreek. 'n Literatuur oorsig van lewenskwaliteit studies in servikskanker word gedoen om toepaslike vraeboë te identifiseer vir Suid Afrikaanse vroue met servikskanker. Opvolgend word die Research and Treatment of Cancer (EORTC) QLQ C30 en CX24 as geskikte vraeboë geïdentifiseer. Die hoofstuk word afgesluit met drie publikasies (eerste outeur GC du Toit) waarin die seleksie van EORTC QLQ C30 en vertaling, yking, psigometriese analise van die EORTC CX24 aangebied word. Die EORTC het amptelike erkenning en sertifisering verleen aan die vertaalde Xhosa en Afrikaanse weergawes van EORTC CX24.

Hoofstuk 2

'n Literatuuroorsig van mediese faktore se invloed op lewenskwaliteit van vroue met servikskanker word aangebied. Spesifieke faktore wat bespreek word sluit in: ouderdom tydens diagnose, stadium van siekte, behandeling en meegaande siekte insluitende verworwe immuuniteitsgebreksindroom. Die wisselwerking tussen hierdie faktore en die voorkoms van servikskanker word toegelig. Die patofisiologie van die behandelings metodes (chirurgie, bestraling, chemoterapie en kombinasies) en die rol in lewenskwaliteit van die onderskeie metodes word geanaliseer. Die oorsig beklemtoon die dissosiasie tussen objektiewe mediese bewysde komplikasies en die pasiënt se lewenskwaliteit.

Hoofstuk 3

Die literatuuroorsig bespreek die kontekstuele faktore wat lewenskwaliteit van vroue met servikskanker beïnvloed. Hierdie faktore sluit in ras, sosio-ekonomiese status en opvoedingspeil. Die wisselwerking tussen die faktore en die insidensie van servikskanker word bespreek. Die spesifieke rol van ras verwante faktore bv. eerste seksuele kontak en aanvanklik presentering met servikskanker en die meegaande impak op lewenskwaliteit word bespreek.

Hoofstuk 4

Oorspronklike navorsing word aangebied as 'n prospektiewe studie oor die lewenskwaliteit van vroue wat presenter met servikskanker. Die invloed van mediese en kontekstuele faktore op die verskillende lewenskwaliteit domeine word geanaliseer. Die verskille in lewenskwaliteit uitkomst tussen vroue wat radioterapie teenoor chemo-radioterapie ontvang het identifiseer die onderskeidende uitkomst in spesifieke areas bv. pyn. Die hoofstuk word aangebied as 'n gepubliseerde artikel(eerste outeur GC du Toit).

Hoofstuk 5

Oorspronklike navorsing word aangebied as 'n transvers studie wat die invloed van kontekstuele faktore op die lewenskwaliteit van menslike immuuniteitsgebrek virus (MIV) positiewe vroue met nuut gediagnoseerde servikskanker is. 'n Tweede, prospektiewe studie beskryf die demografiese eienskappe en lewenskwaliteit van MIV-positiewe vroue met servikskanker wat behandeling ontvang. Die demografiese en lewenskwaliteit verskille tussen MIV-positiewe en MIV-negatiewe voor en na voltooiing van behandeling word beskryf.

Die hoofstuk word aangebied as twee gepubliseerde artikels(eerste outeur GC du Toit).

Hoofstuk 6

Die hoofstuk bied oorspronklike navorsing as 'n transvers studie van kontekstuele lewenskwaliteit van servikskanker oorlewers 18 maande na voltooiing van behandeling. Die invloed van onderskeie kontekstuele en mediese faktore op lewenskwaliteit word geanaliseer.

Hoofstuk 7

‘n Literatuuroorsig oor kwalitatiewe navorsing en servikskanker word bespreek. Die teorie en metodes betrokke by kwalitatiewe navorsing word bespreek. ‘n literatuur oorsig oor vroue se kwalitatiewe ervaring van die verskillende aspekte van servikskanker word bespreek. Die aspekte dek primêre en sekondêre voorkoming soos verteenwoordig deur menslike papillomavirus (MPV) inenting en servikale sitologie. Die invloed van tersiêre aspekte op vroue met servikskanker se ervaring word bespreek na aanleiding van diagnose, behandeling en die gevolge daarvan. Die hoofstuk illustreer die ooreenkomste en verskille tussen kwantitatiewe en kwalitatiewe navorsing.

Hoofstuk 8

Die oorspronklike navorsing van vroue met servikskanker se geleefde ervaring word as eksplorerende kwalitatiewe studie aangebied. Die navorsing gebruik tematiese analise van die vroue se unieke ervaring van servikskanker. Die vroue se ervaring word geanaliseer aan hand van die Kübler-Ross model. Die sielkundige aspekte wat verband hou met die reaksie tot spanning word bespreek aan hand van verdedigings meganismes en hanterings meganismes. Die bespreking onderstreep die teenstrydighede van verdedigings meganismes en hanterings meganismes deur die vroue in die situasie.

Hoofstuk 9

Die verhandeling kom tot die gevolgtrekking dat lewenskwaliteit beoordeling behoort deel uit te maak van kliniese praktyk. Vroue met gevorderde servikskanker het beperkte prognose. Die invloed van hulle persoonlike kontekstuele faktore moet deel wees van besluitneming tydens behandeling. MIV-positiewe status dien nie as uitsluiting tot spesifieke behandelings metodes nie ,maar ,behandeling moet oordeelkundig aangewend word om lewenskwaliteit te verbeter. Toepaslike sielkundige ondersteuning behoort verskaf te word tydens sorg van vroue met servikskanker.

Introduction to the thesis

The introduction to the thesis provides the background and rationale for the thesis. An explanation is provided to the objectives and intentions of the thesis. The thesis is presented as nine chapters including overviews of relevant literature, followed by reporting of original research and concluding with conclusions and recommendations. The thesis represents interdisciplinary and transdisciplinary research that encompasses linguistic aspects of identification, translation, validation and confirmation of psychometric properties of translated versions of EORTC QLQ CX24. These translated versions are then used to describe the effects of the contextual factors on the quality of life of women with newly diagnosed cervical cancer in a prospective study. A transversal study is done on cervical cancer survivors to assess the influence of contextual factors. The contextual factors studied are age, race, education, employment, marital status, stage of disease, treatment and HIV status. A qualitative component is added to enable to represent women diagnosed with cervical cancer to describe their experience.

Background

1.1 Advanced cervical cancer treatment

Advanced-stage cervical cancer remains prevalent in developing countries. South Africa has an incidence of 26.8/100 000.⁽¹⁾ The advanced stage is not amenable to surgery, and radiation therapy was the treatment of choice.⁽²⁾ Based on five randomised controlled trials, the National Cancer Institute (NCI), in 1995, recommended chemo-radiation therapy to be the preferred treatment for locally advanced stage cervical cancer.⁽³⁾ A meta-analysis by Green et al. of available studies in 2001 showed a five-year survival benefit of 29%, in all stages of cervical cancer for chemo-radiation therapy, in comparison to radiation therapy alone.⁽⁴⁾ In a separate meta-analysis Lukka et al., in 2002, calculated a 26% survival benefit, but owing to limitations of the analysis, e.g. omission of unpublished studies, their findings were challenged.^(5,6) A

Cochrane review calculated a survival benefit of 13% across all stages of cervical cancer that was treated with chemo-radiation therapy.⁽⁷⁾ Limitations in all these meta-analyses were differences in study designs, accrual rates, and treatment schedules. Further limitations include the heterogeneity of the control arms of the studies, including the use of previously conducted studies as controls. These limitations were addressed by performing an individual patient data analysis. This individual patient data analysis concluded a 9% survival benefit of chemo-radiation therapy for all stages of cervical cancer. There was a decreasing effect of chemoradiation therapy on survival with increasing stage, with an estimated absolute survival benefit of 10% (stage IA to IIA), 7% (stage IIB) and 3% (stage III to IVA) at 5 years.⁽⁸⁾ Despite documented survival benefit, the use of chemo-radiation therapy comes with a caveat. The initial recommendation of the NCI of chemo-radiation therapy as the preferred treatment of locally advanced cervical cancer, was based on studies conducted on patients with no para-aortic lymph node metastasis. All randomised controlled trials cited by the NCI had para-aortic lymph node metastasis as an exclusion criteria.⁽³⁾ Para-aortic lymph node metastases occur in 16-38% in stage III and IV cervical cancer.⁽⁹⁾ The majority of advanced cervical cancer cases occur in resource-constraint developing countries. Curative chemoradiation therapy, as treatment, would require routine imaging of the para-aortic area to identify patients requiring para-aortic radiation. Resource constraints on imaging facilities pose problems.⁽¹⁰⁾ The Cochrane review of individual patient analysis, which calculated benefit for survival and disease-free survival of chemo-radiation therapy in stage III and IVA cervical cancer, are not statistically significant.⁽¹¹⁾ Despite increased toxicity, chemo-radiation therapy is accepted as a treatment on a widespread basis. The increased toxicity relates to specifically increased grade three and four haematological toxicity (two-fold increases) and gastrointestinal (three-fold increases) events in the chemoradiation therapy group.⁽¹²⁾ The presences of physician recorded toxicity correlate poorly with the patient-reported QOL.⁽¹³⁾ A meta-analysis of chemo-radiation

therapy's toxicity suggests that although the acute toxicity was acceptable, studies on the toxicity-related impact on the QOL are needed.⁽¹²⁾

1.2 Cervical cancer and Acquired Immune Deficiency Syndrome

Acquired Immune Deficiency Syndrome (AIDS) is an important co-morbid disease in cases of cervical cancer in South Africa. Cervical cancer is an AIDS-defining condition (World Health Organisation stage IV).⁽¹⁴⁾ The South African population has 12-18% incidence of Human Immunodeficiency Virus (HIV) infection positivity.⁽¹⁵⁾ The high incidence (7.2-21.8%) of HIV-positive women with cervical cancer in South Africa compromise treatment.⁽¹⁶⁻¹⁸⁾ HIV positive women tolerate the addition of chemotherapy to radiation therapy poorly, and this impacts on completion of treatment with resultant decreased response.^(19,20) AIDS-associated peripheral neuropathy and the use of cisplatin chemotherapy (as part of chemo-radiation therapy) may further compromise the QOL. Cisplatin may lead to, in a dose-dependent fashion, peripheral neuropathy (PN) in the stocking-glove distribution. Peripheral neuropathy (PN) in HIV-infected persons occurs in 50 to 60% of cases. Antiretroviral medication, particularly didanosine, zalcitabine, and stavudine are directly neurotoxic and result in PN identical to AIDS-associated neuropathy. The disease and its treatment synergistically increase PN.⁽¹⁹⁾ In a study of 333 women with locally advanced cervical cancer commencing with chemo-radiation therapy, 53.1% of HIV-positive and 74.6% of HIV-negative women completed \geq four weeks of platinum-based treatment. The chemotherapy component was the most difficult aspect of chemo-radiation therapy for HIV-positive women to complete. Due to these findings, Simmonds suggests the possible omission of chemotherapy in HIV-positive women with cervical cancer as it would result in timely completion of the full dose of radiation therapy.⁽¹⁸⁾

1.3 Contextual factors and QOL

The biopsychosocial model views QOL as an individual's integration of physical aspects such as symptoms of illness or wellness, psychological aspects such as emotional responses and

beliefs, and social aspects such as interpersonal relationships and social support. The QOL is influenced by the biomedical factors of the stage of disease, treatment, and co-morbid disease.⁽²¹⁾ The social circumstances of an individual woman's life further impact their QOL. The traditional QOL-assessment studies focus on a disease-centered paradigm and do not include contextual factors such as cultural and socio-economic circumstances of cancer patients. Ashing-Giwa introduced the concept of contextual QOL as a comprehensive framework including medical and non-medical, patient-related factors such as social and financial position. Relevant social factors may include but are not limited to ethnicity, socioeconomic status, and educational levels. The concept of contextual factors creates a broader framework, including educational levels and socioeconomic status, to assess the QOL. The inclusion of these contextual domains increases the validity and utility of the QOL framework to assess the overall functioning among ethnically and socioeconomically diverse cancer patients.⁽²²⁾

1.4 Qualitative research

The QOL studies relies on quantitative analysis of questionnaire that are developed and validated for specific diseases. These questionnaires consist of a set of predetermined constructs and may not reflect the priorities of the patient in their experience of the disease and its treatment. Qualitative research employing a patient-determined narrative allows for a personalised documentation of patient's priorities and experiences. Combining qualitative patient-experience with the quantitative QOL, research broadens the insight into a holistic approach to patient care. Previously reported combined qualitative and quantitative research on a defined sample of people highlight the reciprocal support of the two approaches.⁽²³⁾

1.5 Aims and proposed scope of research

The appropriateness of chemoradiation therapy versus radiation therapy, as a treatment for advanced cervical cancer in the absence of survival benefit, raises questions with regard to the

impact on the QOL of the two treatment modalities. The co-occurrence of HIV in women with cervical cancer has further impact on treatment and QOL.

The research aims to evaluate the contextual factors influencing the QOL of cervical cancer patients. The initial phase of the study identifies the appropriate questionnaires to be used. The EORTC QLQ CX24 is identified and translated into the indigenous languages of isiXhosa and Afrikaans and is then psychometrically evaluated. The contextual factors of age, race, educational level, employment status, income and marital status, stage of disease, treatment and HIV-status are included in the analysis as possible confounding variables that influence the QOL domains. These factors are studied in a prospective manner, on newly diagnosed women with cervical cancer and in a second, cross-sectional study on survivors of cervical cancer. In the prospective study a subanalysis is done on the specific role of HIV status on the quality of life of newly diagnosed women with cervical cancer. To reflect on the individual perspectives of women, a qualitative study is performed, which documents the lived experiences of women with cervical cancer.

1.6 Hypothesis

Null hypothesis: The contextual factors of age, race, educational level, employment status, income and marital status, stage of disease, treatment and HIV-status does not influence the QOL of cervical cancer cases.

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Chapter 1. The choice of an appropriate questionnaire for QOL studies in South African women with cervical carcinoma

1 Introduction

1.1 Background

The World Health Organisation declared health to be “A state of complete physical, mental and social well-being and not merely the absence of disease.” This definition recognises and stresses the importance of physical, mental and social dimensions in the context of a disease.⁽¹⁾ Traditional assessment of diseases concentrates on objective clinical outcomes such as biological response to treatment, cure or survival. Recently, clinicians and patients alike have argued that subjective indicators should be considered during the assessment of diseases. These subjective indicators are the patient-reported QOL. QOL becomes relevant in oncology when treatment- associated side effects are weighed against survival benefits. In cases of limited survival and where palliative treatment is used, QOL replaces survival as the primary goal. Advanced stage of cervical carcinoma at presentation of recurrent disease, subsequent to primary treatment, have limited prognosis. QOL in this situation is important in considering treatment decisions. Advanced cervical carcinoma occurs predominantly in developing countries. In these countries, advanced stage at presentation causes high mortality rates. A South African example of this is a 35% five-year survival of advanced stage cervical carcinoma (IIIB).⁽²⁾ The world age- standardised incidence rate of 15.2/100 000 with an age-standardised mortality rate of 7.8/100 000 serves as a reference point. In the developing countries, the corresponding figures are an age- standardised incidence rate of 17.7/100 000 and age-standardised mortality rate of 9.7/100 000. The respective figures of 9.0/100 000 and 3.2/100 000 in developed countries are the result of national screening programmes with efficient detection and treatment of premalignant lesions. The predominance of early-stage disease in developed countries, e.g. the United States of America (USA), is reflected by an age-standardised mortality rate of 1.7/100 000. Southern

Africa has an age-standardised incidence rate of 26.8/100 000 with 14.8/100 000 standardised mortality rate (Table 1).⁽³⁾

Table 1. *Age-standardised incidence rates (ASIR), and **age-standardised mortality rates (ASMIR) of cervical cancer.⁽³⁾

	ASIR*(per 100 000)	ASMIR**(per 100 000)
World	15.2	7.8
Developed Countries.	9.0	3.2
Developing Countries	17.7	9.7
Southern Africa	26.8	14.8
South-Central Asia	24.5	14
South-Eastern Asia	15.8	8.3
North America	5.7	1.7

1.2 Reasons for QOL studies

Aaronson identifies three areas where the QOL assessment would be relevant. These include the following: a) documentation of the consequence of disease and treatment on QOL b) effect on the QOL in studies comparing the clinical effectiveness of different treatment options c) evaluation of the QOL studies in the clinical management of patients.⁽⁴⁾

1.2.1 Documentation of the consequence of disease and treatment, on the QOL

Langedijk identified xerostomia and dysphagia as radiation therapy-related factors that adversely affect the QOL in cases of the head- and neck cancers.⁽⁵⁾ This study resulted in treatment adaptation of regime, with a reduction in radiation therapy dose and better-directed

radiation therapy, to reduce the aforementioned toxicities. Identification of changes in QOL allow patients and healthcare workers to make an informed decision with regards to treatment options.⁽⁵⁾ Effective communication with patients leads to better patient preparedness, their cases where treatment-related QOL changes occur. Changes in treatment regimens lead to improvement in the QOL.

1.2.2 Effect on QOL in studies comparing the clinical effectiveness of different treatments

Early stage breast cancer treated by mastectomy and breast-conserving therapy has equivalent survival figures. A long-term QOL study of 315 women with an early-stage breast cancer documented superior QOL of cases treated with breast-conserving therapy. These women had better physical and role functioning at one year in comparison to the mastectomy group. The mastectomy group, in comparison to the conservative managed patients, were sexually less active and had reduced body image at one year. The breast-conserving therapy group had continued improvement in overall QOL and psychological well-being up to five years after diagnosis.⁽⁶⁾ The above study underlines that in cases of equivalent survival benefits of different treatment options, effects achieved is of a decisive nature. QOL, as a secondary outcome measure in this situation, serves as a primary decision factor.

1.2.3 Evaluation of QOL studies in the clinical management of patients.

Objective assessment of the QOL allows healthcare workers to address specific areas that must be addressed with tailored supportive care. Fayers emphasize the indications for the QOL studies described by Aaronson and adds the following indications: a) QOL assessment in clinical trials with palliative intent b) assessment of the QOL in long-term cancer survivors c) QOL used as a prognostic factor.⁽⁷⁾ Ashing-Giwa expands on the use of QOL studies by introducing contextual QOL.⁽⁸⁾

1.2.4 QOL assessment in clinical trials with palliative intent

Advanced cancer are commonly associated with nausea, anorexia, weakness and fatigue. In a placebo-controlled randomised trial Beller concluded that Megestrol acetate improves, as a dose dependent drug, appetite, mood and overall QOL of the patient in the palliative care of advance endocrine-insensitive tumours. The study included 240 patients randomised to placebo or Megestrol acetate. Significant statistical improvement is documented in the Megestrol acetate group in the QOL domains of mood, appetite and overall QOL.⁽⁹⁾ In a situation of palliative treatment, QOL is a primary outcome measure, and comparative treatments are assessed for the efficacy of relief of symptoms.

1.2.5 Assessment of quality of life in long-term cancer survivors

Improved survival, due to early detection and effective treatment of cancer, results in increased numbers of long-term cancer survivors. Treatment-related reactions result in long-term sequelae. Thirty percent of head and neck cancer long-term survivors report dryness of the mouth and high psychological distress levels up seven to ten years after treatment.⁽⁵⁾ A further example of the QOL in long-term survivors is patients with gestational trophoblastic neoplasia. Gestational trophoblastic neoplasia a chemosensitive condition with high cure rates. The long-term psychosocial sequel in women diagnosed with gestational trophoblastic neoplasia demonstrated good QOL with comparative physical, social and emotional functioning compared to their healthy counterparts. Despite the good QOL, 50% of women with previous diagnosis gestational trophoblastic neoplasia, expressed a need to participate in counselling with regards to psychosexual issues and 74% stated that they would have joined support groups if was offered during treatment. This wish for the psychosexual support was expressed five to

ten years subsequent to the diagnosis of gestational trophoblastic neoplasia.⁽¹⁰⁾ QOL assessment in long-term cancer survivors allows for appropriate support and enhanced QOL.

1.2.6 QOL as prognostic factor

Ferrandina in a chemotherapy trial identified pre-treatment QOL as a significant prognostic factor in 991 patients diagnosed with recurrent, persistent or advanced stage (IVB) cervical carcinoma. The pre-treatment patient-reported physical well-being (PWB) as measured by the PWB subscale of the FACT-CX is significantly associated with survival in advanced cervical cancer trials, even after controlling for known prognostic factors in this study.⁽¹¹⁾ QOL assessment can thus predict survival and influence treatment decisions.

1.2.7 Contextual QOL studies.

QOL assessment should take cognisance of the patient's cultural and socioeconomic status. Ashing-Giwa introduced the concept of contextual QOL as a comprehensive framework including non-medical, patient-related factors such as social and financial position.⁽¹³⁾ Contextual QOL was developed to expand the traditional QOL framework to include the cultural and socioeconomic status of patients in assessing their QOL. The inclusion of these contextual domains increases the validity and utility of the QOL framework to assess the overall functioning among ethnically and socioeconomically diverse cancer patients. Contextual factors in this framework include, amongst other, socioecological factors, cultural background, demographic details and the health care system available to the patient.⁽¹²⁾ Contextual QOL factors, identified in breast carcinoma patients, could be improved with interventions such as community-based support groups.⁽¹³⁾

1.3 Terminology:

A range of methods is available for measuring the QOL. A variety of terms describes this QOL measurement instruments. The Federal Drug Administration in the United States of America adopted the term ‘patient-reported outcome measurements’. Health outcome assessment has been put forward as a further alternative. Walters set the convention to refer to the well-established term of QOL measurement instruments or questionnaires.⁽¹⁴⁾ The term QOL questionnaire is used in this dissertation.

QOL measurement is done with questionnaires, consisting of multiple questions. Questions are referred to as items, and different domains of QOL are assessed by single items or multi-item scales. The European Organisation for the Research and Treatment of Cancer (EORTC) QOL Questionnaire Core 30(QLQ-C30) illustrate single item scales of dyspnoea (Question 8) and multi-item scales of emotional functions (Questions 9, 10 and 11).⁽¹⁵⁾

1.4 Criteria for selection of QOL measurement instruments

1.4.1 *Health Technology Assessment Program*

The Health Technology Assessment Program reviewed the literature of QOL questionnaires used in clinical trials. They identified and recommended the following criteria in the selection of questionnaires (Table 2).⁽¹⁶⁾

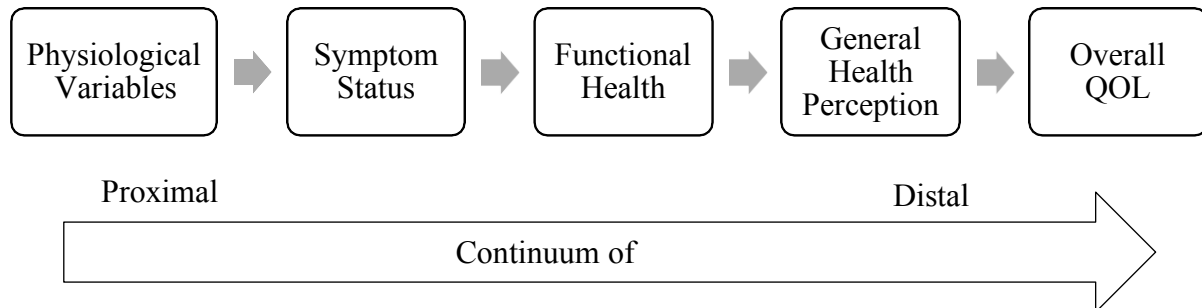
Table 2. Selection criteria for questionnaires ⁽¹⁶⁾

Criteria	Questions to be addressed
Appropriateness	Is the content of the questionnaire appropriate to the questions that the clinical trial is intended to address?
Reliability	Does the questionnaire produce results that are reproducible and internally consistent?
Validity	Does the questionnaire measure what it claims to measure?
Responsiveness	Does the questionnaire detect changes over time that matter to patients?
Precision	How precise are the scores of the questionnaire?
Interpretability	How interpretable are the scores of the questionnaire?
Acceptability	Is the questionnaire acceptable to patients?
Feasibility	Is the easy to administer and process?

These criteria are applicable to all questionnaire used in clinical trials. To address the specific selection process in oncology trials, Luckett discusses important factors in the choice of the questionnaire and confirms the Health Technology Assessment Program criteria.⁽¹⁷⁾ In the setting of QOL as a primary outcome, Luckett alludes to the importance of Wilson and Cleary mode, at different levels of QOL questionnaires.⁽¹⁸⁾

1.4.2 Wilson and Cleary's conceptual model of health QOL.

This model describes the relationship amongst the various aspects of health. The model is schematically depicted in Diagram 1.

Diagram 1. Conceptual model of health-related quality of health (18)

This conceptual model integrates the Biomedical and Social Science paradigms of health aspects. In isolation, the biomedical paradigm focuses on the spectrum of etiological agents, pathological processes with results in physiological and clinical outcomes. This paradigm integrates the philosophical view of reductionism and mind/body dualism. Reductionism implies that a complex phenomenon is ultimately derived from a single primary principle. The mind/body dualism doctrine separates mental and somatic phenomena. In contrast to the biomedical paradigm, the social science paradigm emphasizes functional and overall wellbeing. This emphasis includes the social context in which the patient lives and social support systems to deal with disease and illness associated disruption of it.

1.4.3 Structural equation modelling

The integration of these two aforementioned paradigms into Wilson and Cleary's model makes it a useful tool for healthcare providers. The theoretical model of Wilson and Cleary was evaluated by Sousa et al., utilizing the structural equation modelling. Structural equation modelling is a statistical technique for establishing a causal relationship between factors, by means of a combination of statistical data and qualitative causal symptoms. Sousa analysed variables of 917 patients living with AIDS. These variables included CD4 counts (physiological variables), a

checklist of AIDS specific symptoms (symptom status), Health Assessment Questionnaire Disability Index questionnaire (functional status), and general health perceptions measured by a visual analogue scale, as well as overall QOL, as assessed by questionnaire. This structured equation modelling analysis of the Wilson and Cleary model validates its usefulness in clinical practice.⁽²⁰⁾

1.4.4 Continuum of proximal to distal QOL questionnaires

According to the Wilson and Carey model, QOL questionnaires can be divided into a continuum of proximal (symptom) based and distal (overall) based. In studies with the QOL as the primary outcome, proximal questionnaires reflect personal, individual and symptom-specific experience. Distal questionnaires reflect the overall QOL. Overall QOL is not only affected by health status, but also by non-medical factors like financial stress. Intermediate questionnaires address the disadvantages of proximal and distal questionnaires but is subject to patient response shift. Patient response shift is a time based, physiological adaptation by patients, in response to changing health. Three kinds of response shift are described.⁽²¹⁾ The first kind of shift is the recalibration of patients' concept of extremes of symptoms. The patient's perception of "worst pain imaginable" may change after a particularly painful medical procedure. The second kind of shift occurs with patient's revision of the value attached to certain life dimensions. In this regard, reprioritisation of existential concerns over physical function at the end of life is an example. Thirdly a shift occurs when patients reconceptualise QOL altogether and focus only on positive aspects of life and ignore declining health concerns.⁽²²⁾ The practical implication is that a proximal (symptom-based) questionnaire is preferable when the QOL is the primary outcome in patients with the disease. Distal questionnaires are effective in comparative studies between diseases and comparative studies in the general healthy population. The use of a combination of proximal and distal questionnaires in studies yields a balanced result. The combination of the EORTC QLQ-C30 with

EORTC Cervix Cancer Module (QLQ CX-24) and Functional Assessment of Cancer Treatment-General (FACT-G) with Functional Assessment of Cancer Treatment-Cervix (FACT-Cx) are examples.

1.5. Quality of life questionnaires

1.5.1 *Generic questionnaires*

Generic questionnaires were initially developed to perform population surveys on the general health status of the population. They were later applied in QOL studies involving diseases. The emphasis of these questionnaires is the measurement of general health. The two most commonly generic questionnaires used are the Sickness Impact Profile and the Nottingham Health Profile.⁽²³⁾

1.5.1.1. Sickness Impact Profile

Berger developed the Sickness Impact Profile as a measurement of perceived health status, as measured by its impact upon the behaviour. The items consist of daily activities, including social functioning. The items are negatively worded, and identify dysfunction. The instrument consists of 136 items and assesses 12 dysfunctional scales. The instrument lacks a global question on QOL.⁽²⁴⁾

1.5.1.2 Nottingham Health Profile

The instrument consists of 38 items and covers six domains of sleep, pain, emotional reaction, social isolation, physical mobility and energy levels. The Nottingham Health Profile is shorter than Sickness Impact Profile and easier to complete. The disadvantage of it includes an emphasis on severe disease state. This emphasis results in minor important changes in health status to loss of sensitivity. .⁽²⁵⁾

1.5.2 Disease-specific questionnaires

Disease-specific questionnaires measure specific proximal domains and have the advantage of focussing on elements unique to a particular disease. This focused approach allows for sensitivity to compare effects of treatment on QOL aspects. A further advantage is its usefulness in comparing the QOL in studies that involve different treatment options. The QLQ-C30 and FACT-G questionnaires are oncology-specific instruments.

1.5.2.1 European Organisation for the Research and Treatment of Cancer

The European Organisation for the Research and Treatment of Cancer (EORTC) was founded in 1962 to conduct, develop and stimulate cancer research in Europe. It has a multi-disciplinary and multi-centred approach to trials. A QOL group was created in 1986, which initiated a research programme to develop an integrated modular evaluation of the QOL clinical trials.

This led to the development of EORTC QLQ-C30 and QLQ-CX24. The 30-item QLQ-C30 version 3 is a psychometrically validated, cross-culturally accepted questionnaire, and it is applicable to a broad spectrum of cancer patients as a core questionnaire. This instrument consists of five function scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea/emesis, and pain), six single-item scales (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea, and financial impact), and global QOL scale.⁽¹⁵⁾

Griemel developed the QLQ CX-24 as a cervical specific module. It was developed in a multi-cultural setting, including nine European Countries, Brazil, Korea and Taiwan.⁽²⁶⁾ The development was completed according to EORTC QOL Group guidelines for module development. Subsequent to the development, validation of the module was conducted in countries with a cross-cultural distribution. Cross-cultural relevance was addressed by means of words that could be widely understood, and were socially acceptable and equivalent across the countries and cultures. Sexual items were the most difficult to translate and adapt to various cultures.⁽²⁷⁾

The 24 items QLQ-CX24 is summarized in three scales, namely symptom experience, body image, and sexual/vaginal functioning. The other dimensions of this questionnaire are single item scales of lymphedema, peripheral neuropathy, menopausal symptoms, sexual worry, sexual activity and sexual enjoyment.

1.5.2.2 Functional assessment of cancer therapy – General

The Functional Assessment of Chronic Illness Therapy Measurement System is a collection of health-related QOL questionnaires targeted at the management of chronic illness. The measurement system, under development since 1987, began with the creation of a generic core questionnaire called the Functional Assessment of Cancer Therapy- General (FACT-G). Cella developed this 27-item questionnaire.⁽²⁸⁾ The initial questionnaire was developed on a multi-national basis in the United States of America, together with 135 patients who were diagnosed with advanced cancer. Validation was completed on the second sample of 630 patients with a variety of cancers of different stages.⁽²⁹⁾ Patients rate items on a five-point scale started from “not at all” to “very much.” The FACT-G version 4 is currently available in 45 different languages. The FACT-G Version 4 is a 27-item compilation of general questions (items). It has four domains: seven items measuring Physical Well-Being, seven items measuring Social/Family Well-Being, six items measuring Emotional Well-Being, and seven items measuring Functional Well-Being. It was validated in 1993. It is appropriate for use with patients with any form of cancer, and extensions of it have been used and validated in Chapter 2, under the section of rheumatoid arthritis).⁽²⁹⁾

1.5.2.3 FACT-Cx

FACT-Cx version 4 comprises the FACT-G with an additional. The FACT-G has four domains: i) Physical Well-Being ii) Social/Family Well-Being, iii) Emotional Well-Being, and iv) Functional Well-Being. The cervical-cancer-specific subscale contains 15 additional items specifically related to cervical cancer and its treatment sequelae.

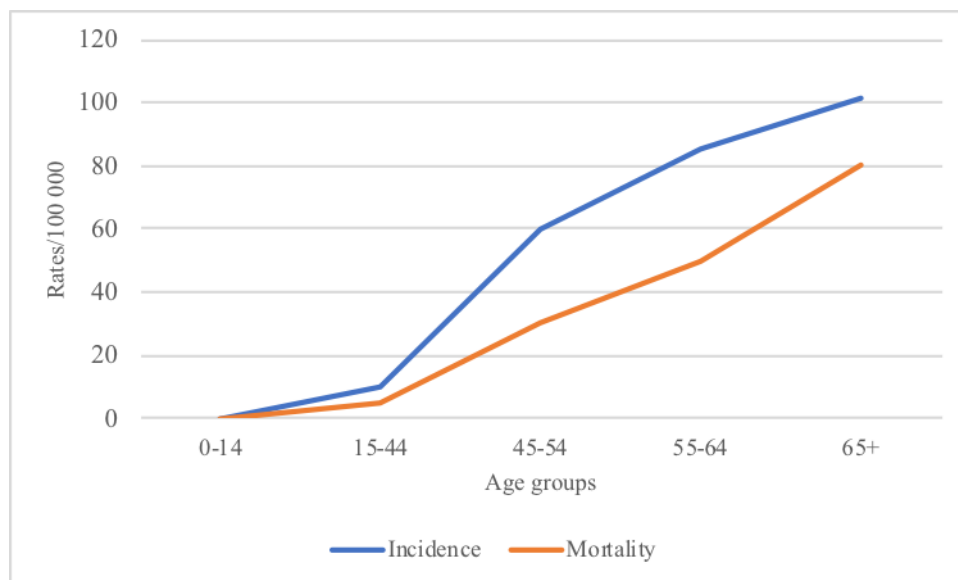
1.6. Study Population

The characteristics of the study population are important in the choice of QOL questionnaires. Cella identifies important study population characteristics that impact the choice of questionnaires. These characteristics are a) age and stage distribution of the disease, b) socioeconomic status and c) co-morbidity. Disease-related factors are a) incidence and b) mortality rates of relevant cancer.⁽²⁸⁾

1.6.1 Incidence

Cancer of the cervix is the second most common cancer among women worldwide. Developing countries contribute 86% of the total the total worldwide caseload. South Africa has a cervical cancer age-specific incidence rate of 26.6/100 000 and 14.5/100 000 age-specific mortality rates. The age-specific incidence groups and mortality rates are depicted in Graph 1.⁽³⁰⁾

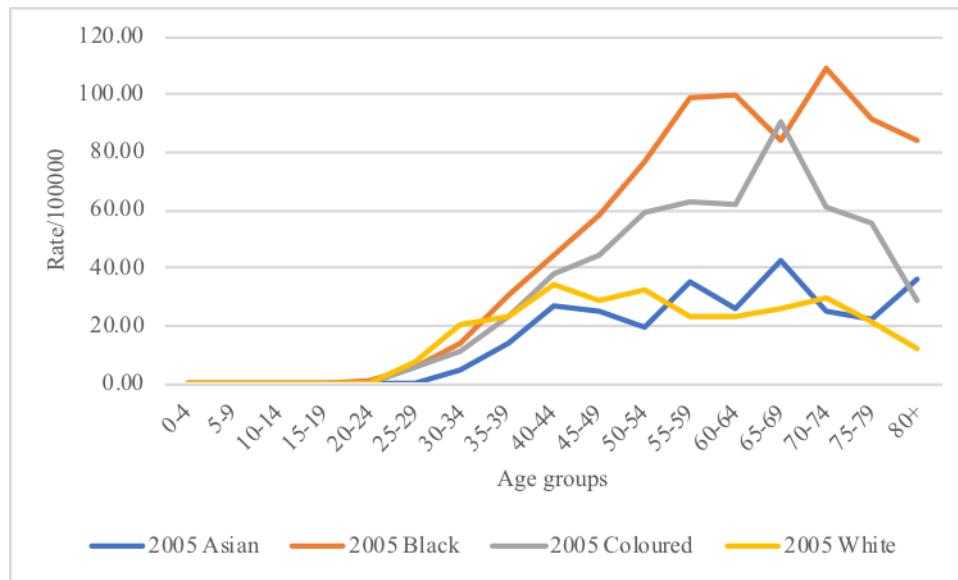
Graph 1. South African cervical cancer incidence and mortality rates ⁽³¹⁾



Accurate data on incidence rates of cervical cancer depend on cancer registries. South Africa launched a pathology based registry in 1986. This registry relied on histological information obtained from private and public laboratories. Initially, 80 laboratories were included and with

the last available report of 2005, a total of 75 laboratories participated. Age-specific incidence rates vary in the different race groups (Graph 2.).⁽³¹⁾

Graph 2. South African racial incidence rates of cervical cancer.



These differences in race incidence are underlined with the estimated lifetime risk for developing of cervical cancer per racial group. The lifetime risk for African women is 1/34 and the corresponding figure for white women is 1/93. Racial classification in health research is a controversial issue. South African disease-specific data document race grouping to correlate with mortality patterns. Sitas documented substantially higher smoking-attributed national mortality rates in the coloured than in the white population. In this study, the hazards from smoking in the coloured population were more than double, in comparison to those in the white population. The higher smoking-attributed mortality of the male and female coloured populations resulted not only from their higher prevalence of smoking but also from their high relative risks of death, comparing smokers with non-smokers. The coloured male population had a higher smoker versus non-smoker relative risk of death from any cause than the white male population, who in turn had a higher relative risk than did the African male population.⁽³²⁾

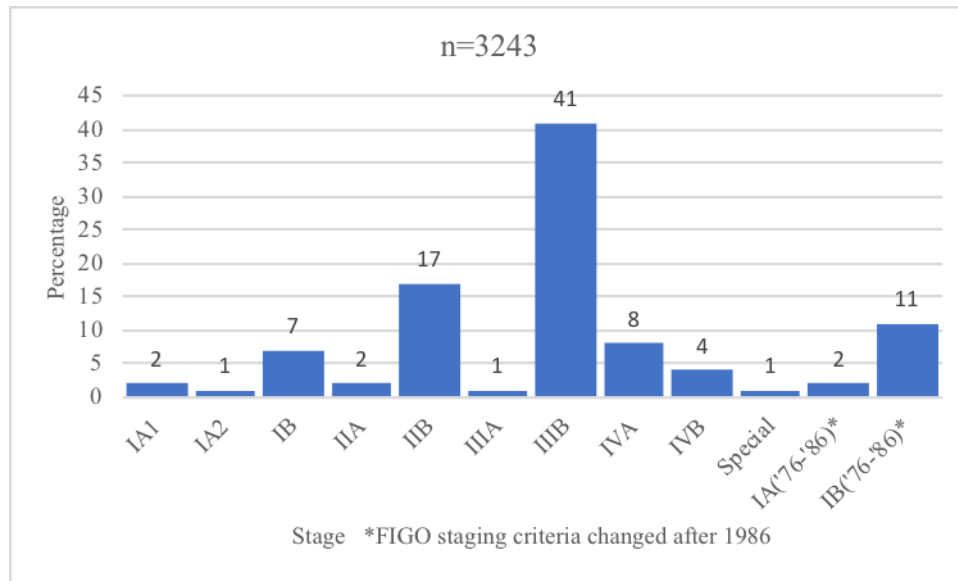
The race is a social construct and not a scientific classification.⁽³³⁾ The ethical aspects of race as a research variable is debated by Van Niekerk. He concludes that the inclusion of race as a research variable should be based on the eventual goal of the study.⁽³⁴⁾ Racial classification is a fraud with difficulties. Self-identification in a population census in the United States of America resulted in 800 000 respondents indicating that they were both black and white.⁽³⁵⁾ In South Africa, the race is a proxy for poor access to healthcare facilities that includes preventative programmes like cervical cytology services. South African disparities in the availability of healthcare are the result of political and historical events. These disparities also exist in the United States of America. In the USA, women at risk for poor cancer-related outcomes are primarily low-income and underserved.⁽³⁶⁾ In particular, Latin-Americans typically experience decreased QOL and increased overall morbidity and comorbidities due to their over-representation among the medically underserved population. Health care disparities in the USA is highlighted by Bloche.⁽³⁷⁾ He concludes that racial and ethnic disparities in health care exist and are associated with worse outcomes. These disparities occur despite corrections for income, education and health insurance status. Further studies underline the disparity occurring in USA healthcare and concludes that long-standing societal discrimination may still exist.⁽³³⁾ High cervical cancer rates in the South African coloured and black population are the result of the disparities in the availability of cervical cytology screening services. Race, as a variable, in South African cervical cancer research is, therefore, the relevant variable.

1.6.2 Stage of disease

Early stages of cervical cancer, diagnosed on routine cytology, is asymptomatic. Advanced disease present itself with symptoms of pain and bleeding. These symptoms have a direct impact on QOL. South African data reveals predominantly advanced stage disease at presentation. Walker et al. found that 66% of women present stage III and IV.⁽³⁸⁾ At Groote

Schuur Hospital, 75 – 80% of women were presented with an advanced disease (stage IIIB and higher).⁽³¹⁾ The stage distribution of a Tygerberg Hospital study for a 16 year period is depicted in Graph 3.⁽³⁹⁾

Graph 3. Cervical cancer stage distribution at Tygerberg Hospital for 1976-1992⁽³⁹⁾



1.6.3 Co-morbidity

Medical conditions like co-morbidity impact the QOL of cervical cancer cases. South Africa has a high incidence of HIV infection.⁽⁴⁰⁾ South African studies on HIV infection incidence in cases of cervical cancer are depicted in Table 3. The impact of HIV infection has multiple effects on women with cervical cancer. These impacts include poor completion rates of radiotherapy in Acquired Immune Deficiency Syndrome cases. More advanced stage of cervical cancer at a presentation in AIDS cases results in poor prognosis. Chemotherapy, as a sensitising agent with radiotherapy, is poorly tolerated by HIV-positive women. HIV-positive women are statistically younger at presentation with cervical cancer. All of the aforementioned factors impact on QOL of cervical cancer cases with AIDS.⁽⁴¹⁾

Table 3. HIV infection incidence in South African cases of cervical cancer
 (*=statistically significant)

Author	n	HIV+ (%)	Mean age(years)		Stage II and IV (%)	
			HIV-	HIV+	HIV-	HIV+
Lomalisa(42)	836	7,2	53*	44*	55	65
Moodley(43)	271	21,8	54*	41*	94	64
Simonds(41)	383	18,2	50*	41*	58*	65*

1.6.4 Language

Language is an expression of culture and individuality of its speakers. It influences the way speakers to perceive their environment. QOL is a perception of the cancer patient's environmental experience. Assessments of QOL require questionnaires in the mother tongue of the patients. This is required to accurately reflect their QOL and therefore translation to indigenous languages of available English questionnaires are necessary.

1.6.4.1 Translational theory

In the South African multilingual culture, it is important that the medical questionnaires used are available in the language of the participating community under investigation. Appropriate translation from the source text to the target text must include the target culture.

Respondents must have a clear, unambiguous understanding of the questions. A standard approach to translation of medical questionnaires include forward translation from the source text to the target text. Subsequent back translation from target text to the source text serves as quality control mechanisms and for detections of errors in meaning. This approach is the

currently recommended and subscribed approach of the EORTC's translational unit.⁽⁴⁴⁾ This standard approach can result in loss of cultural appropriate translations. Jelsma translated the QE-5D (European Quality of Life 5-Dimensions) into Shona with two forward translators.⁽⁴⁵⁾ One translator produced a direct, literal translation, and a second translator produced a target-orientated, colloquial translation. Back translation into the source text resulted in non-equivalence of the two translated versions. However, the target culture understood the second translation better. A lay panel was commissioned to incorporate both approaches. Subsequent to the study of Jelsma, Mkoka translated the QE-5D into Xhosa. Mkoka followed a process that was target culture orientated, and this resulted in a better understanding of the final translation by the target audience.⁽⁴⁶⁾

The office of Minority Health in Chicago set standards for translated texts. This office focuses on health research in a multi-cultural and multi-lingual environment.⁽⁴⁷⁾ This environment requires translations to be culturally competent and linguistically appropriate. The literacy rate of the target culture should be known to the translators. This enables them to produce appropriate, understandable translations for different cultures, age and intellectual groups. The use of unsuitable language, despite being linguistically correct, leads to misunderstanding and concomitant disinformation. Translations of medical questionnaires in South Africa by professional translations are becoming a prerequisite at research institutions. Professional translators should be familiar with the terminology and literacy levels of the target culture. Knowledge of colloquial Afrikaans, spoken by the Cape Coloured community, is particularly relevant in this translational process.⁽⁴⁸⁾

Translation is a complex communication system across multiple cultural, literacy and linguistic levels. There are three distinct translation approaches. They are linguistic, sociolinguistic and the functional approach. Linguistic approaches primarily focus on the content of the source language. The primary focus on the source language may lead to misunderstanding by the

target culture. Socio-linguistic translation refers to the translation process paying specific attention to the organisation and structuring of text in the target culture. Hermanus described socio-linguistic translation as a culturally specific organisation and structuring of texts.⁽⁴⁹⁾ This approach maintains elements of source text linguistics and integrates target text linguistic structuring of text. The functional translation approach, as introduced by Vermeer, focuses on the target culture.⁽⁵⁰⁾ This approach focusses away from the source language, to the intended communication purposes according to the target culture's needs. This functional approach, as described by Vermeer, is further refined and defined by Nord. Nord's translation model includes the seven aspects.⁽⁵¹⁾ These aspects are the use in a variable fashion during translation, and they are:

- 1) a 'pragmatic model,' which accounts for communicative interaction
- 2) a 'culture-oriented model,' which considers the culture-specific behaviour
- 3) a 'consistent model,' to establish a framework that is coherent and provides the guidelines to justify the translator's decisions regarding any translation
- 4) a 'comprehensive model,' that can be applied to all text types
- 5) an 'anti-universalist model,' which allows for culture-specific differences
- 6) a 'practical model,' accounting for all transcultural communication
- 7) an 'expert model,' which awards translators the prestige of being competent and responsible experts in their field

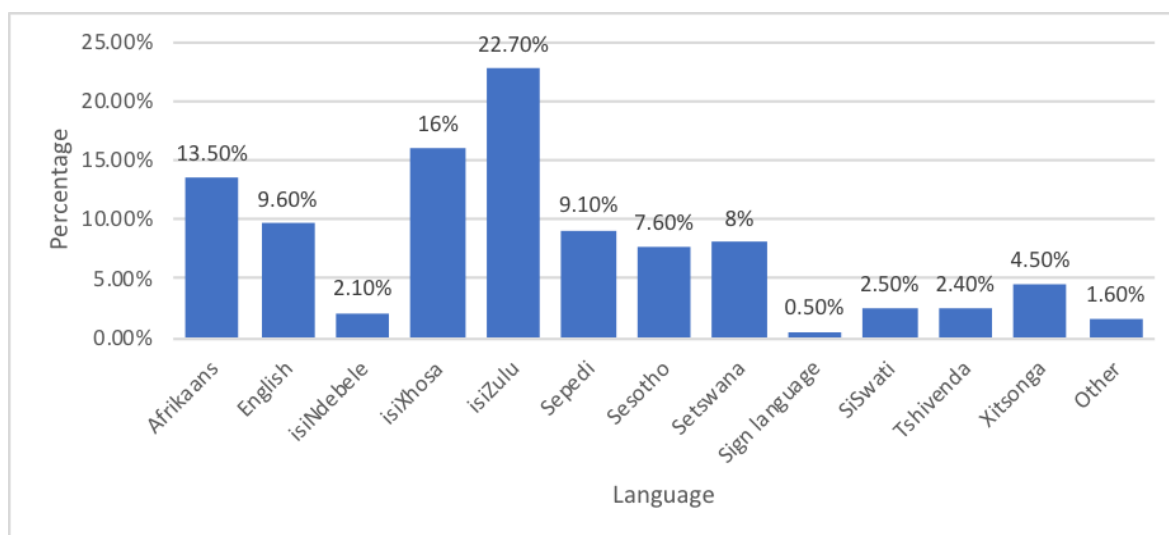
In a South African study, Fourie used the model of Vermeer and Nord. Fourie studied a cohort of learners attending secondary schools in the Cape Peninsula.⁽⁵²⁾ The cohort included 50 grade 11 learners, speaking colloquial Afrikaans and the second group of 50 Xhosa-speaking learners. Using an AIDS questionnaire, the study involved an Afrikaans and Xhosa translations of the original English questionnaire. Two separate translational approaches were used. The first set of translation used a linguistic approach. The second translation from the

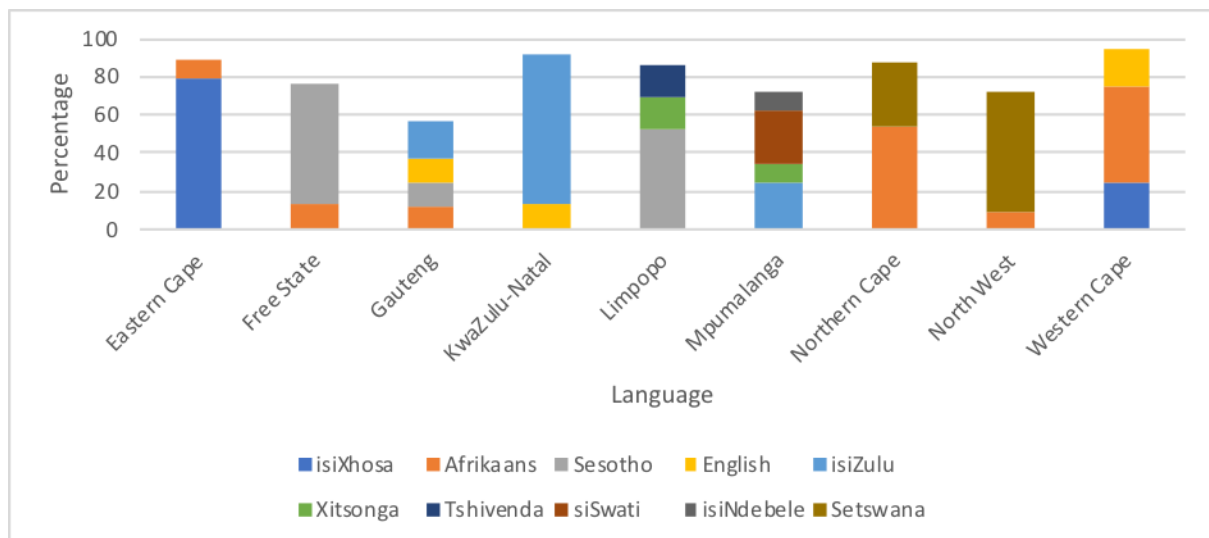
English questionnaire used a functional approach. The study concluded that the functional approach led to more effective communication than the linguistic approach. The translator and target audience should have shared knowledge of the target language and follow the same general linguistic rules. Fourie concludes that back translation to source text may be omitted in the translation process especially if the trained translators are familiar with the subject matter. The forwarded translated text should be assessed and passed by a panel of people comprising of the target culture audience.

1.6.4.2 Language distribution

South Africa has 11 official languages, and the distribution is geographically defined. Graph 3 shows the language distributions in South Africa and Graph 4 depicts the provincial distributions of these languages.⁽⁴⁹⁾

Graph 3. South African language distribution



Graph 4. South African provincial language distribution

1.7. Systemic overview of available studies of QOL in cervical cancer

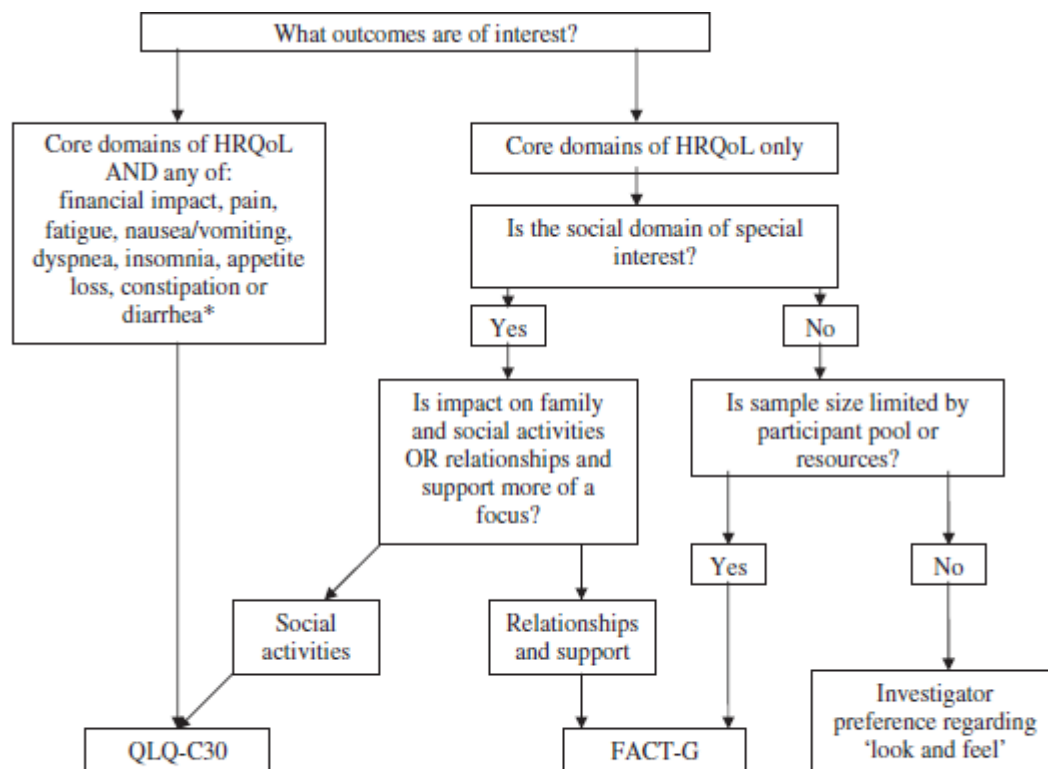
The two most widely used combinations of generic and cancer specific questionnaires are the EORTC QLQ-C30/QLQ-CX24 and the FACT-G/FACT-Cx. Luckett evaluated the EORTC QLQ-C30 and FACT-G questionnaires to guide clinicians in their choice between the two.⁽¹⁷⁾ Studies, using the two questionnaires, were included if the criteria of reporting on the reliability, validity and responsiveness of the questionnaires were met. These inclusion criteria re-affirm the criteria set by Health Technology Assessment Program.⁽¹⁶⁾ The studies were evaluated on psychometric properties and interpretability. In concluding Luckett proposed an algorithm to choose a questionnaire (Figure 1).⁽¹⁷⁾

An alternative approach to selection of questionnaires is the use of criteria to assess the properties of the questionnaires.⁽⁵³⁾ Terwee et al propose the use of psychometric properties according to a predefined set of criteria. These proposed criteria form part of COSMIN (Consensus-based standards for the selection of health Measurement instrument) and include (a) content validity, (b) internal consistency, (c) criterion validity, (d) construct validity, (e)

reproducibility, (f) responsiveness, (g) floor and ceiling effects, and (h) interpretability. To resolve controversies and disagreements on the various definitions included in COSMIN further consensus reports were required ⁽⁵⁴⁾ Considerable overlap exists with the COSMIN and Health Technology Assessment Program criteria.

The two approaches to criteria-based selection (Terwee) and outcomes based (Lockett) are both valid and mutually complementary ^(17,54). The current overview to select an appropriate questionnaire used the algorithm proposed by Lockett.

Figure 1. Algorithm in the selection of questionnaire ⁽¹⁷⁾



*Where cognitive functioning is an outcome of interest, researchers are encouraged to seek a dedicated questionnaire rather than rely on the scale included in the QLQ-C30.

This algorithm refers to general oncology trials. In addressing the issue of gynaecological specific malignancies, a further systemic review of available questionnaires used in specific gynaecological oncology trials was performed. Lockett found that both EORTC and FACT

gynaecological sub-modules complied with Health Technology Assessment Program criteria. ^{(17,}

⁵⁴⁾ This systemic review did not include the FACT-CX. The selected questionnaires for QOL studies in South African women with cervical cancer should be applicable in a study group with high prevalence of advanced disease and meet the study group's specific language preferences.

1.7.1 Methods and Material

A systemic overview was completed on articles using EORTC QLQ-C30/QLQ-CX24 or FACT-G /FACT-CX in cases of cervical cancer. Relevant articles were identified by searches in PubMed EBSCO host Research Databases and Google Scholar. The keywords used in the search included cervical cancer, cervical carcinoma and QOL. Further articles were identified via the reference lists of returned articles. Results were limited to articles subsequent to 1993, the year in which the original validation articles on FACT-G and EORTC QLQ-C30 were published. The current systemic overview focussed on specific characteristics of the studies. They were the study design (prospective or cross-sectional), QOL outcome (primary or secondary outcome point), and timing of QOL assessment during the disease process and nationality of the study population.

1.7.2 Results

The database research identified ten articles using the FACT-G/CX as questionnaire and 14 using the EORTC questionnaires (Table 4 page 49).

With regards to the study design, both questionnaires have been used in cross-sectional and prospective studies. All the EORTC based studies used QOL as the primary outcome of the FACT-G/CX questionnaires, showing 50% split between primary and secondary outcome endpoints (Table 5).

Table 5. Study design and endpoints in articles.

Questionnaire	Study design		QOL Endpoint	
	Cross-section	Prospective	Primary	Secondary
EORTC QLQ-C30/CX-24 n=14	10 articles	4 articles	14 articles	0 articles
FACT-G/Cx n=10	6 articles	4 articles	5 articles	5 articles

Despite a number of articles published on both questionnaires, care should be exercised in the interpretation of the number study participants. It should be noted that three articles using the EORTC QLQ-C30/CX questionnaire described various aspects of QOL of the same study population consisting of 860 Korean women with cervical cancer. Two studies from Italy using the EORTC report on the same study population. In the case of FACT-G/CX questionnaires, the Gynaecological Oncology Group reports QOL in four separate articles on chemotherapy use in advance recurring and persistent disease. The Gynaecological Oncology Group Combines the QOL data from the four studies in a further article describing the QOL as pre-treatment prognostic factor.

Nationalities of the study populations using the EORTC QLQ-C30/QLQ-CX24 include a spectrum of populations including multi-national European, Korean, Sri-Lankan, Dutch, German, Thailand, Italian, French and Polish. Study populations in articles using the FACT-G/CX were United State of America, Chinese, Philippine and Australian. The timing of the questionnaires in both EORTC group and FACT groups ranged from pre-treatment to long-term post-treatment follow-up.

1.7.3 Discussion

The systemic overview compared EORTC QLQ-C30/QLQ-CX24 to FACT-G/CX as the possible QOL questionnaires in South African women with cervical cancer. Both questionnaires have been extensively used in a large number of cervical cancer cases. The main difference is the use in studies with the QOL as the primary outcome measure. In all EORTC studies, QOL was the primary outcome measure. This is in comparison to the FACT-G/CX studies where the QOL was primary outcome measure in 50 %. A study by Cella illustrates the importance of QOL as a primary outcome measure.⁽⁵⁵⁾ He describes the QOL, as a secondary outcome measure, in four cisplatin-based chemotherapy regimens for stage IVB, recurrent and persistent cervical cancer cases (Gynaecology Oncology Group Study 204). The study used the PC (paclitaxel and cisplatin) as the reference group to evaluate the efficacy of the three other chemotherapy arms. These arms were VC (vinorelbine and cisplatin), GC (gemcitabine and cisplatin) and TC (topotecan and cisplatin). An interim analysis performed four years after commencement of the study revealed that none of the experimental arms was superior to PC and the study was, therefore, terminated. The result was a total of 434 eligible patients (72% of the initial accrual target) available for survival analysis. QOL analysis could be performed on 363 patients (60% of the initial accrual target). This resulted in a reduction of power of QOL assessments from 85 – 55%.⁽⁵⁵⁾ Based on the above, QOL as a secondary outcome measure is compromised due to treatment-related premature termination of the study.

An important aspect is the nationality of the study population in which the questionnaires were used. Nationality may serve as a proxy for the incidence of cervical cancer (Table 1).

The FACT-G/CX has been predominantly used in United States of America studies. The majority of these studies are on cases with stage IVB disease, as well as recurrent and persistent cervical cancer.⁽⁵⁵⁾ Use of the FACT-G/CX in developed countries, e.g. the Philippines and China identified culturally associated deficiencies and both these studies suggest that further cultural adaptation of

the questionnaires. ^(57,58) The EORTC has been used in both developed and developing countries and has been found culturally acceptable in a diverse population e.g. Korea, Sri-Lanka and Thailand.^(28,59) These developing countries have a similar incidence of cervical cancer in South Africa. A cultural important aspect is that the EORTC QLQ-C30 and QLQCX-24 are available the prevailing indigenous languages (Afrikaans, English and isiXhosa) in the Western Cape. (Graph) This is not the case with the FACT-G/CX.

1.7.4 Conclusion

The appropriate questionnaire for QOL studies in South African women with cervical cancer should be available in the language of the patients and should have been used in previous studies with the QOL as primary outcome measure. The questionnaire should also have been used in a population with high prevalence of advanced stage of cervical cancer. The EORTC-QLQ-C30/QLQ-CX24 meet these requirements and therefore is selected as the appropriate questionnaire. The validation of the isiXhosa and Afrikaans translated versions of the QLQ-CX24 and its further evaluation of its psychometric properties in the study population serves as a further justification for its selection.

Table 4. Available articles using EORTC QLQ-C30/QLQ-CX24 and FACT-G/Cx in cervical cancer.

Author	Cases	Questionnaire	Study design	QOL outcome	Timing of questionnaire	Country
Garana (56,56)	Not stated	FACT-Cx	Cross section	Primary	3 months post- treatment	Philippines
Long (57)	186	FACT-Cx FACT/GOG- NTX* BPI**	Prospective	Secondary	Pre-treatment Prior to 2 nd chemo therapy Week 13 9 months post-treatment	USA
McQuellon (58)	252	FACT-Cx BPI-SF	Prospective	Secondary	Pre-treatment Prior to cycles 2,3,4.	USA
Du (59)	22	FACT-G	Cross section	Primary	Not stated	China
Park (60)	860	QLQC30 CX24	QLQ- Cross section	Primary	1.4-22 years post-treatment	Korea
Beesley (61)	195	FACT-G	Cross section	Primary	Not stated	Australia
Jayasekara (27)	112	QLQ-CX24	Cross section	Primary	3 months post-treatment	Sri Lanka
Shin(62)	860	QLQ-C30 QLQ-CX24	Cross section	Primary	1.4-22 years post-treatment	Korea

Ashing-Giwa (12)	560	SF-12,FACT-G/CX	Cross section	Primary	1-5 years post diagnosis	USA
Dong (63)	860	QLQ-CX24	Cross section	Primary	1.4-22 years post-treatment	Korea
Griemel (64)	121	QLQ-C30 QLQ-Cx24	Cross section	Primary	7,3 monthsandlongerpost-treatment	Multi-national
Korfage (65)	291	SF-36 QLQ-CX24	Cross section	Primary	2-10 years post diagnosis	Netherland
Cella (66)	434	FACT-Cx FACT/GOG#	Prospective	Secondary	Pre-treatment Prior to 2 nd chemo therapy Week 13 9 months post-treatment*	USA
Singer (67)	134	QLQ-CX24 QLQ-C30 HADS	Cross section	Primary	Post surgery	Germany
Swangvaree (68)	100	QLQ-C30 QLQ-CX24	Cross section	Primary	At diagnosis	Thailand
Downs (69)	28	FACT-Cx	Prospective	Secondary	Pre-treatment	USA

					Post-cycle 3 and 6	
Plotti (70)	33	QLQ-CX24	Cross section	Primary	24 months post treatment	Italy
Bjelic-Radisic (71)	346	QLQ C30 QLQ-CX24	Prospective	Primary	During and post-treatment	Multi-national
Chase(2012)	991	FACT-Cx	Cross-section	Secondary	Pre-treatment	USA
Ding (72)	400	FACT-Cx	Cross section	Primary	Pre-treatment to 5 years post-treatment	China
Ferrandina (11)	227	QLQ 30,QLQ-CX24 HADS##	Prospective	Primary	Pre-treatment 3,6,12 months post-treatment	Italy
Le Borgne (73)	173	QLQ 30,QLQ_CX 24	Cross section	Primary	5-15 years post-treatment	France
Mantegna (74)	169	QLQ 30,QLQ-CX24 HADS##	Prospective	Primary	Pre-treatment 3,6,12,24 months post-treatment	Italy
Pasek (75)	157	QLQ 30	Prospective	Primary	Pre-treatment Immediate post-treatment Six months post-treatment	Poland

* Neurotoxicity Subscale

** Brief Pain Inventory # Gynecologic Oncology Group (FACT/GOG) four-item neurotoxicity scale ###Hospital Anxiety and Depression Scale

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Articles related to Chapter 1

The first page of each original publication is included. The selection of an appropriate questionnaire was published. The EORTC CX24 was available in English. Consent was obtained from EORTC to translate this questionnaire into the local languages of Xhosa and Afrikaans. Following EORTC translation guidelines the questionnaire was translated and validated. This resulted in the second article. The analysis of psychometric properties of the translated versions is presented as a third publication.

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Die identifisering van 'n geskikte vraelys vir die bepaling van lewenskwaliteit by Suid-Afrikaanse vroue met servikskanker

Author:
George du Toit¹

Affiliation:
¹Department of Obstetrics and Gynaecology, Stellenbosch University, South Africa

Correspondence to:
George du Toit

Email:
dutoitg@worldonline.co.za

Postal address:
Van der Stelstraat 50, Stellenbosch 7600, South Africa

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Servikskanker is een van die algemeenste kankertipes onder Suid-Afrikaanse vroue. In die afwesigheid van 'n voldoende voorkomende servikale sitologieprogram presenter die meerderheid vroue met servikskanker in 'n gevorderde stadium. Die prognose van dié vroue, ondanks terapie, is beperk. Menslike immuuniteitsgebrek virus-infeksie (MIV-infeksie) benadeel die behandeling van servikale kanker. Servikskanker, en die behandeling daarvan, het 'n impak op die lewenskwaliteit van die vroue. Die objektiewe bepaling van lewenskwaliteit kan lei tot aanpassing van behandeling, asook toepaslike ondersteuning. Hierdie studie is gedoen om die mees geskikte vraelys vir Suid-Afrikaanse vroue met servikskanker te identifiseer. Die twee vraelys wat internasionaal die meeste gebruik word, is die *European Organisation for the Research and Treatment of Cancer (EORTC)* en die *Functional Assessment of Chronic Illness Therapy Measurement System (FACIT)*. Deur die sistematiese ondersoek van gepubliseerde artikels is die twee vraelys aan die hand van spesifieke kenmerke geëvalueer. Hierdie kenmerke sluit in: studiestruktuur (dwarsnit of prospektief), lewenskwaliteitsuitkoms (primêr of sekondêr), tydstop van gebruik tydens die siekte en die nasionaliteit van die studiebevolking. Gebaseer op hierdie kenmerke is die EORTC as die mees geskikte vraelys geïdentifiseer.

The choice of an appropriate questionnaire for quality of life studies in South African women with cervical cancer. Cervical cancer is one of the commonest cancers among South African women. In the absence of an adequate, preventative cervical cytology programme, the majority of women present with an advanced stage of disease. Despite treatment, the prognosis for these women is poor. Furthermore, HIV and AIDS impacts adversely on the treatment of cervical cancer, whereas cervical cancer and its treatment again affect the quality of life. Objective assessment of the quality of life can improve treatment and supportive care. The current study was done to identify the most appropriate questionnaire to assess the quality of life experienced by South African women with cervical cancer. The European Organisation for the Research and Treatment of Cancer (EORTC) and the Functional Assessment of Chronic Illness Therapy Measurement System (FACIT) questionnaires are the most commonly used for assessment of the quality of life patients with cancer have. The current study assessed the appropriateness of these questionnaires for use in South Africa on the following criteria: study structure (prospective or transverse), quality of life endpoint (primary or secondary), timing of assessment during disease process and the nationalities of the study populations. The EORTC questionnaire was identified as the most appropriate for application to South African women with cervical cancer.

Inleiding

Agtergrond tot servikskanker in Suid-Afrika

Servikskanker verteenwoordig 18% van alle nuut gediagnoseerde kanker gevalle onder Suid-Afrikaanse vroue. Die ouderdomspesifieke insidensie van servikskanker in Suid-Afrika is 26.8 per 100 000 vroue (Arbyn *et al.* 2011). Hierdie statistiek is in teenstelling met die VSA, wat 'n ouderdomspesifieke insidensie van 5.7 per 100 000 vroue het (Arbyn *et al.* 2011). Weens die feit dat vroue nie gereeld die nasionale servikale siftingstoets deur middel van servikale smere ondergaan nie, kom 'n verhoogde insidensie van dié tipe kanker voor onder Suid-Afrikaanse vroue (Denny 2012). Figuur 1 toon die Suid-Afrikaanse ouderdomspesifieke insidensie en mortaliteitskoers van servikskanker aan (*World Health Organization* [WHO] 2010). Hand aan hand met die gevorderde stadium gaan die hoë mortaliteitskoers van 14.8 per 100 000. Die vergelykende syfer in die VSA is 1.7 per 100 000.

Original Research: Translation and validation of European Organisation for Research and Treatment of Cancer

Translation and validation of European Organisation for Research and Treatment of Cancer QLQ-CX24 questionnaire into the indigenous African languages of *isiXhosa* and Afrikaans

Du Toit GC, MChB, MMed, FCOG/LKOG(SA), Part-Time Consultant

Unit of Gynaecological Oncology, Tygerberg Hospital, University of Stellenbosch

Nel DG, Part-Time Consultant, Centre for Statistical Consultation, University of Stellenbosch

Correspondence to: George du Toit, e-mail: dutoitg@worldonline.co.za

Keywords: quality of life assessment, European Organisation for Research and Treatment of Cancer QLQ-CX24 questionnaire, translation, Afrikaans, Xhosa

Abstract

Objectives: Quality of life (QOL) assessment plays an important role in oncological clinical practice and research settings when evaluating treatment outcome. Cervical cancer remains a prevalent disease in South African women. The current study translated and validated the European Organisation for Research and Treatment of Cancer (EORTC) cervical cancer module, QLQ-CX24, into *isiXhosa* and Afrikaans and validated the questionnaires.

Setting and subjects: The QLQ-CX24 was translated forwards into *isiXhosa* and Afrikaans and backwards into English and then reconciled by four independent language practitioners. The translated version was completed by 15 *isiXhosa*- and 15 Afrikaans-speaking patients with cervical cancer. Cronbach's alpha coefficient, a measure of internal consistency of response, was calculated. The conversion validity was evaluated by assessing the correlation between each item and its scale. Discriminant validity was examined by comparing the correlation values of each item with other scales using Pearson's and Spearman's correlation coefficients.

Results: The translated *isiXhosa* and Afrikaans questionnaires demonstrated good conversion validity in the multi-item scales with values of Cronbach's alpha coefficient ≥ 7 . Discriminant validity was demonstrated in the single-item questions. Patients completed the questionnaires in less than 20 minutes.

Conclusion: The translated *isiXhosa* and Afrikaans version of QLQ-CX24 was successfully translated and validated and is available for research and clinical use.

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Introduction

South Africa has a high incidence of cervical cancer (26.6/100 000) and disease-associated mortality (14.5/100 000).¹ A previous study showed advanced stage of presentation in the majority of cases with five-year survival of 35% in stage III disease.² Advanced stage of disease at presentation results in considerable disease- and treatment-related morbidity.³ Quality of life (QOL) in patients afflicted by cancer has become a major determinant in deciding treatment options and it has become an integral part of oncology practise and research. The European Organisation for Research and Treatment of Cancer (EORTC) has a generic questionnaire (QLQ-30 version 3) that assesses the general quality of life of all cases of malignancy.⁴ A specific mode for cervical cancer (QLQ-CX24) has been developed and has been used in clinical research. The

QLQ-30 is available in Afrikaans, *isiXhosa* and *isiZulu*, but the QLQ-CX24 questionnaire is not. The QLQ-CX24 consists of three multi-item scales and six single items that are not assessed by the core instrument (QLQ-30). Multi-items in QLQ-CX24 scales are symptom scales (questions 31-37, 39 and 41), body image (questions 45-47) and sexual and vaginal function (questions 50-53). The questionnaire allows for four options of response to each question (Table I).⁵

Method

The English version of the questionnaire was translated into *isiXhosa* and Afrikaans according to the EORTC criteria. The original items were translated from English into *isiXhosa* and Afrikaans by two independent language practitioners through a process of forward translations, resolution and backward translation by

An analysis of the psychometric properties of the translated versions of the European Organisation for the Research and Treatment of Cancer QLQ CX24 questionnaire in the two South African indigenous languages of Xhosa and Afrikaans

G.C. DU TOIT, MBCHB, MMED, FCOG/LKOG(SA), PART-TIME CONSULTANT, Unit of Gynaecological Oncology, Tygerberg Hospital, University of Stellenbosch, Stellenbosch & M. KIDD, PHD, CONSULTANT, Centre for Statistical Consultation, University of Stellenbosch, Stellenbosch, South Africa

DU TOIT G.C. & KIDD M. (2015) *European Journal of Cancer Care*

An analysis of the psychometric properties of the translated versions of the European Organisation for the Research and Treatment of Cancer QLQ CX24 questionnaire in the two South African indigenous languages of Xhosa and Afrikaans

This study evaluates the psychometric properties of the Xhosa and Afrikaans version, the European Organization for Research and Treatment of Cancer (EORTC) of the Quality of Life Questionnaire Cervical Cancer Module (QLQ-CX24). Translated Xhosa and Afrikaans versions, EORTC QLQ-CX24 and the core questionnaire (the EORTC QLQ-C30) were completed by 66 Xhosa and 142 Afrikaans speaking women newly diagnosed with cervical cancer. Construct reliability and validity of the EORTC QLQ-CX24 questionnaire were assessed via factor analysis, multi-trait scaling analyses and known group comparisons. The mean age was similar in the groups with a mean age of the Xhosa group (52 year) and Afrikaans group (49.2 year) ($P = 0.25$). The study groups had a high unemployment rate of, respectively, 52% (Xhosa) and 51% (Afrikaans) ($P = 0.35$). The Xhosa group had a statistically significant higher incidence of advanced stage (III and IV) disease ($P = 0.006$). Scale reliability was confirmed by Cronbach's α coefficients for internal consistency, which ranged from 0.73 to 0.81 (Xhosa) and 0.73 to 0.76 (Afrikaans). Clinical validity of both language versions was demonstrated by the ability to discriminate among different stages of cervical cancer. The translated Xhosa and Afrikaans versions of the EORTC QLQ-CX24 were found to be reliable and valid measure of quality of life of women with cervical cancer.

Keywords: cervical cancer, quality of life.

INTRODUCTION

Cervical cancer is the most common cancer in Southern Africa women with a 26.8 per 100 000 incidence rate and

a mortality rate of 14.8 per 100 000 (Arbyn *et al.* 2011). The majority of women present with advanced stage disease and limited survival, despite treatment (du Toit & Smit 1997; Ali *et al.* 2012). Quality of life in these circumstances is important in treatment decisions. The measurement of quality of life in women with cervical cancer involves questions related to sexual functioning. Specific culture-associated terms exist to describe sexuality and bodily function. Due to these factors, assessment of the quality of life of these women must be in their language (Cain *et al.* 2011). South Africa is a multicultural and

Correspondence address: George du Toit, Unit of Gynaecological Oncology, Tygerberg Hospital, University of Stellenbosch, Stellenbosch, South Africa (e-mail: dutoitg@worldonline.co.za).

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Chapter 2. Quality of life and medical factors

2 Introduction

Medical, disease-related factors and contextual, patient-related factors influence QOL of women with cervical cancer. Medical factors include age of patients, stage of cancer; treatment and comorbidities e.g. acquired immune deficiency syndrome. In this chapter, the influence of these various factors on the quality of life of women with cervical cancer will be described and illustrated with examples from the literature.

2.1 Age

The interaction of physical factors and psychosocial development determine the QOL of a person. Erikson describes eight stages of psychosocial development through which a healthy developing human should pass from infancy to late adulthood (Table 1).⁽¹⁾ Each stage is characterized by conflicting forces and requires an individual to negotiate and reconcile these forces. The forces include biological, social and cultural factors. The QOL of a woman is the result of her psychosocial development and the challenges of a particular developmental phase. Cervical cancer and its treatment may disrupt a woman's normal psychological maturation and achievement goals. These disruptions lead to different responses and emotional experiences of the affected woman and her QOL.

Table 1. Psychosocial development stages. ⁽¹⁾

Stage	Basic Conflict	Important Events	Outcome
Infancy (Birth- 18 months)	Trust vs. Mistrust	Feeding	Children develop a sense of trust when caregivers provide reliability, care, and affection. The lack of this will lead to mistrust.

Early Childhood (2-3 years)	Autonomy vs. Shame and Doubt	Toilet Training	Children need to develop a sense of personal control over physical skills and a sense of independence. Success leads to feelings of autonomy, failure results in feelings of shame and doubt.
Preschool (3-5 years)	Initiative vs. Guilt	Exploration	Children need to begin asserting control and power over the environment. Success in this stage leads to a sense of purpose. Children who try to exert too much power experience disapproval, resulting in a sense of guilt.
School Age (6-11 years)	Industry vs. Inferiority	School	Children need to cope with new social and academic demands. Success leads to a sense of competence while failure results in feelings of inferiority
Adolescence (12-18 years)	Identity vs. Role Confusion	Social Relationships	Teens need to develop a sense of self and personal identity. Success leads to the ability to stay true to yourself while failure leads to role confusion and a weak sense of self.

Young Adulthood (19- 40 years)	Intimacy vs. Isolation	Relationships	Young adults need to form intimate, loving relationships with other people. Success leads to healthy relationships while failure results in loneliness and isolation.
Middle Adulthood (40- 65 years)	Generatively vs. Stagnation	Work and Parenthood	Adults need to create or nurture things that will outlast them, often by having children or creating a positive change that benefits other people. Success leads to feelings of usefulness and accomplishment while failure results in shallow involvement in the world
Maturity (65- death)	Ego Integrity vs. Despair	Reflection on Life	Older adults need to look back on life and feel a sense of fulfilment. Success at this stage leads to feelings of wisdom while failure results in regret, bitterness, and despair.

Erikson's theory is based on psychosocial development and have received criticism due to lack of attention to emotional and cognitive development. Further criticisms of Erikson's theory include focus on ambiguous terminology, incomplete descriptions of the psychosocial stages, and poorly supported claims of male-female personality differences based on biological

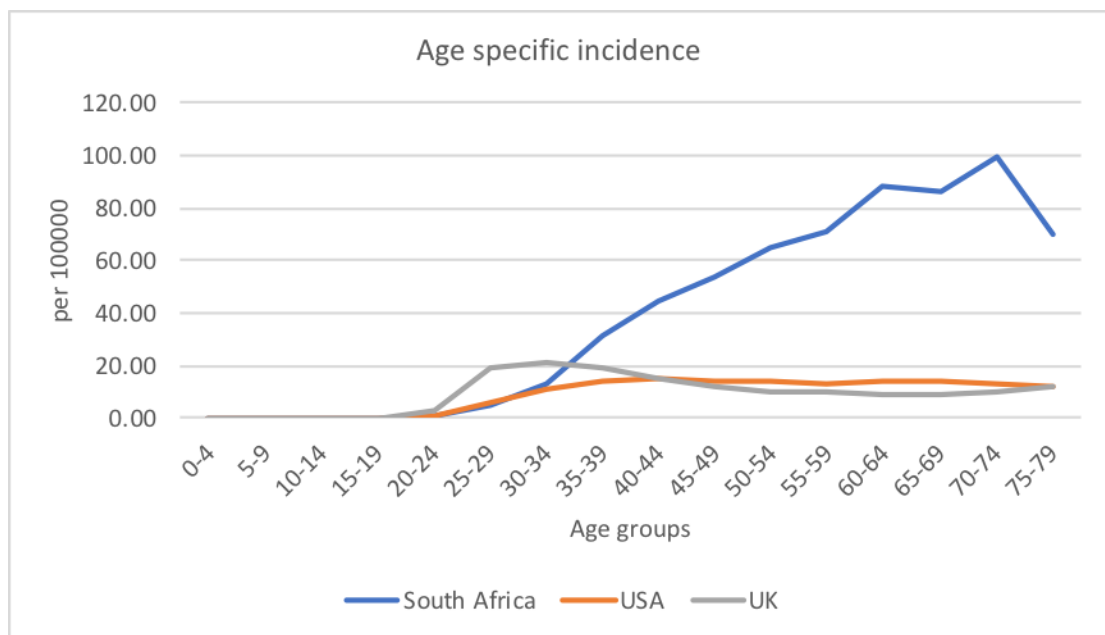
factors. Erik Erikson never acquired academic credentials e.g. degree or tertiary qualification. This made his work the easy target for criticism, yet the prominence of his theories demonstrates that even without academic training, Erikson's ideas were not only valid, but original and significant.⁽²⁾

2.1.1 Age-specific incidence rates

The age of presentation with cervical cancer is the result of the interplay of epidemiological and health system factors. Epidemiological factors include the age of coitarche, multiple sexual partners, smoking and concomitant disease e.g. HIV infection / AIDS. Health system factors, e.g. cervical cytology smears allow for appropriate intervention on pre-malignant condition with the subsequent decrease in numbers of invasive cancer. Age of coitarche varies with population groups. In parts of sub-Sahara Africa age of female coitarche is reported as 12, 6 years.⁽³⁾ Corresponding age in Nigeria is 12, 3 years.⁽⁴⁾ South African studies report age of coitarche between 16 to 18 years depending on rural or urban study populations.⁽⁵⁾ The age of coitarche varies over time between, and within cultures. A cross-sectional Norwegian study from 1987 to 2002 describes a median age of female coitarche of 17,8 years with a decline of 2,3 years in age over time.⁽⁶⁾ The association of low socioeconomic status and poor education with early coitarche are documented in developed and developing countries. In a study of eight African countries (Botswana, Kenya, Namibia, Senegal, Swaziland, Uganda, Zambia and Zimbabwe) coitarche before 15 years was statistically significant in girls with a history of several factors. These factors were alcohol use, tobacco, drug use, truancy, poor parental or guardian connectedness, sedentary behaviour, having been in a physical fight and seriously injured, mental distress and poor economic status.⁽⁴⁾ In the Norwegian population women from lower socioeconomic status experienced coitarche one year earlier than their higher socioeconomic counterpart.⁽⁶⁾ Cervical cytology services are a health system factor influencing the age of women presenting with cervical cancer. The varying degree of cervical cytology

services amongst countries account for the variation of age-specific incidence of cervical cancer as reflected in Graph 1. The high age-specific incidence in South Africa in comparison to the United Kingdom and the United States of America is the result of organised screening programmes in the latter two countries vs. poor screening in the former. ⁽⁷⁾

Graph 1. Age specific incidence rates ⁽⁷⁾



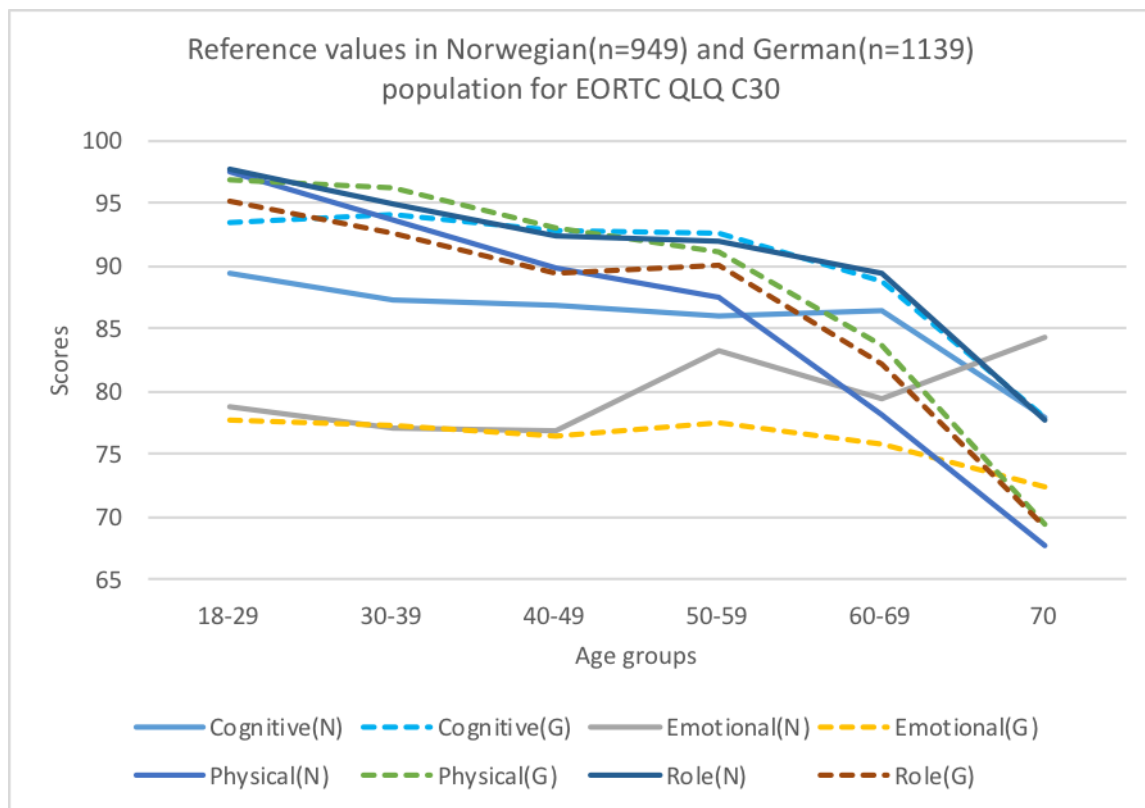
The demographics of cervical cancer in the United States of America has changed in a 25-year timespan. The Surveillance, Epidemiology, and End Results analysis documents a decrease in both localized and advanced cases of cervical cancer. The current United States of America population of women with cervical cancer are younger and are more likely to be of Asian or Pacific Islander descent in comparison to 25 years ago.⁽⁸⁾ The increasing population of pre-menopausal women with cervical cancer emphasises the priority of fertility preservation treatment. Successful completion of cancer treatment with preservation of fertility influence the QOL of these women.

2.1.2 Age and QOL

2.1.2.1 QOL and age in a healthy population

The physical and emotional needs and priorities of the population changes with increasing age. Reprioritisation of goals is age dependent. The reprioritisation affects certain domains of QOL in the healthy general population concurrently with age. In studies from Germany and Norway, the European Organisation for the Research and Treatment of Cancer QLQ-C30 questionnaire was administered to sample of the general population. Both studies aimed to obtain reference values in the healthy, cancer-free population. Age-related changes in the various domains of QOL are represented in the Graph 2. The mean values for the domains of cognitive function, physical and role functioning shows age-related decline in QOL. In the age groups of 50 years and older the Norwegian population had an increase in the emotional domain. The German population, of the same age groups, in comparison to this, shows in decline in this domain. These two studies documented age-related changes in QOL of the general population and illustrated differences between countries.^(9,10) The impact of QOL in a healthy population should be kept in mind in assessing the age-related changes in the QOL of women with cervical cancer.

Graph 2. Reference values of European Organisation for the Research and Treatment of Cancer QLQ C30 for the general population in Norway (N) and Germany (G). ^(9,10)



2.1.2.2 Age and QOL

Women with cervical cancer may have different responses, feelings and QOL depending on the psychosocial developmental stage they are experiencing. Young adult women (19-40 years) are in the initial stage of building relationships with subsequent establishment of her family, career, self-identity and sexual image. A diagnosis of cervical cancer in these women threatens reproductive function and adversely affects their QOL. For mothers diagnosed with cervical cancer, their QOL is significantly compromised due to their impaired physical and psychological role function. Their inability to care for their children leads to guilt, distress and anxiety. Cancer treatment may lead to decrease in their work performance with the loss of personal achievement, self-identity, social networks and financial security. Adult women (40-65 years) have achieved career and family goals as well as greater financial security. Forced, early retirement related to cervical cancer and its treatment disrupted financial and social

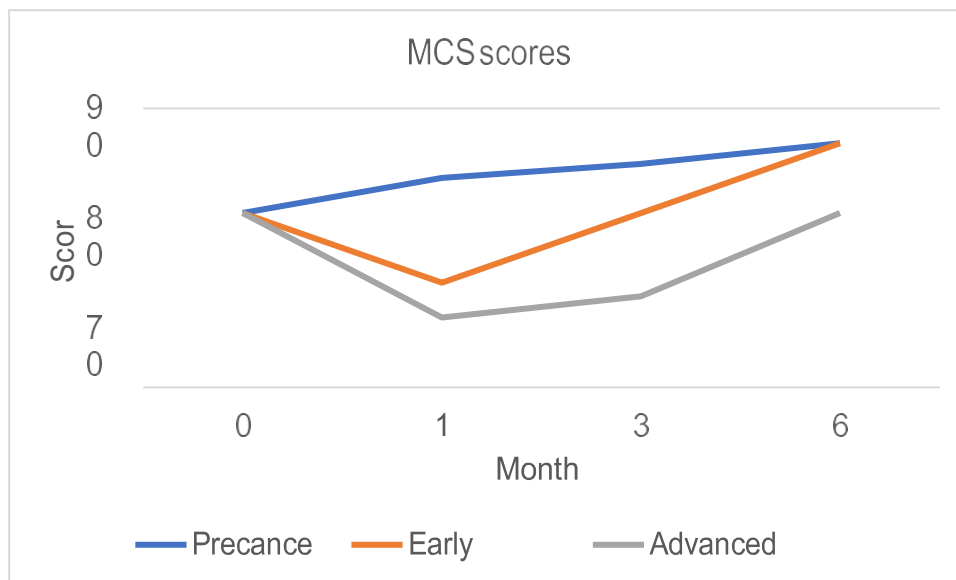
security and decreased the QOL in these domains. Their inability to fulfil their social role to care for their family leads to distress. Women in their middle age have to adapt to the age-related physical changes and sexual function. Cervical cancer and its treatment further threaten their self-image. Mature women (65 years to death) have greater acceptance of cancer diagnosis. Their retirement status allows for flexibility to adapt their daily routine to treatment e.g. radiotherapy sessions. Co-morbid disease e.g. degenerative disease such as arthritis results in the decrease of QOL. Decreased social activity with loneliness and depression are prevalent in the ageing population. ⁽¹¹⁾ A cross-sectional Italian study of 115 women with cervical cancer used the SF 36 questionnaire to assess the QOL. With the exception of physical functioning young women, had the worse QOL in all domains. This counterintuitive increase in QOL with age underscores the aggressive impact on QOL of young women with cervical cancer. ⁽¹²⁾ In contrast to the Italian study a Chinese study of 173 women with cervical cancer, with the exception of social functioning, reported no difference in levels of QOL amongst the various age groups. The older women reported worse social functioning in comparison to their younger counterparts. The Chinese study used World Health Organisation QOL Scale –Hong Kong version. ⁽¹¹⁾ Cultural differences in the approach to cancer between the Chinese and Italian study offers a plausible explanation for the age-related different QOL outcomes.

2.2 Stage and treatment

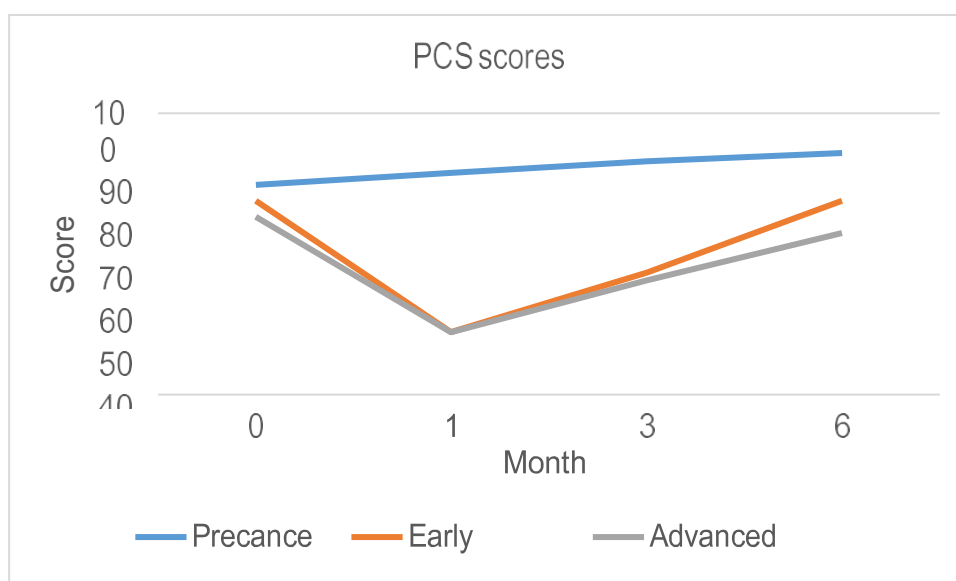
The stage of a cervical cancer determines treatment. The QOL of the patient is the combined result of the initial influence of the disease with subsequent treatment-related influence. The staging of the disease is an objective system determined by the medical fraternity while the QOL is the subjective experience of the patient. The patient may be unaware of the stage of the disease. However, symptoms experienced by the patient impact on the QOL experience.

The effects of stage of disease on QOL is best reflected by assessment prior to the commencement of treatment. A comparative Chinese study of 92 patients with precancerous lesions (CIN II, III), 93 patients with early-stage cervical cancer (stages I-IIA) and 35 patients with advanced cervical cancer (stages IIB and higher) address these effects. Using the Short Form Health Survey (Chinese version) questionnaire prior to treatment this study documents differences in the physical component summary and mental component summary categories of QOL in the various groups. ⁽¹⁴⁾ The results of the study appear in Graph 3 and 4.

Graph 3. Mental component summary (MCS) scores. ⁽¹³⁾



Graph 4. Physical component summary (PCS) scores ⁽¹³⁾



Pre-treatment physical component summary scores are statistically significantly different ($p=0,008$) between the three groups. Mental component summary scores are similar for the three groups. The difference in physical component summary scores occurs due to the presence of troublesome symptoms in advanced stage cancer and the absence of symptoms in the early stage group. The physical component summary scores of the pre-cancerous group improved over the study period. Treatment-related decline physical component summary scores in early-stage cancer and advanced stage cancer groups in comparison to the precancer group are related to chemotherapy and radiation therapy. The mental component summary score was not statistically different between these two groups over the study period. Despite the statistically significant difference in age of the three groups, it had no influence on the QOL. The study concludes that the stage has a significant impact on QOL as reflected by the pre-treatment differences. Treatment, as dictated by stage, has an impact on QOL with time as reflected by an initial decrease at one-month follow-up in physical component summary scores in early stage and advanced stage cervical cancer. ⁽¹³⁾

2.2.1 Hysterectomy

The surgical extent of hysterectomy for early-stage cervical cancer and benign disease is similar. Data on QOL with the various surgical approaches to hysterectomy for early-stage cervical cancer is lacking. QOL of hysterectomy done for benign disease offers guidelines in this aspect. A systemic review of 30 papers reported on the QOL differences in randomised controlled trials of abdominal and laparoscopic hysterectomy. Seven studies reported QOL as secondary outcomes. Only two studies used validated questionnaires, and the review concluded better QOL in laparoscopic hysterectomy for the first six weeks after surgery.⁽¹⁴⁾ There was no difference in the QOL beyond this point. An important aspect of this study is the exclusion of women with enlarged uteri. In this systemic review, a study by Garry was identified as a hallmark study that leads to the conclusion of improved QOL in the laparoscopic hysterectomy

group.⁽¹⁵⁾ Despite the better QOL in the laparoscopic hysterectomy group, Donnez, commenting on the study by Garry, pointed out that complication rates, with the possible impact of QOL, were significantly higher in the United Kingdom in comparison to Belgium for laparoscopic hysterectomy.⁽¹⁶⁾ The higher complication rates were related to the initial learning curve of the surgeons in the United Kingdom. Subsequently to the aforementioned systemic review, a Cochrane systemic review of the various surgical approaches to hysterectomy included 34 studies of 4495 women. Table 3 reflects the main findings of this review. The review concluded that women whom laparoscopic hysterectomy had a better QOL in comparison to women who had an abdominal hysterectomy or vaginal hysterectomy. This difference was present up to two months postoperatively.⁽¹⁷⁾

Table 3 (17) *Please see separate page at end of chapter.*

The inclusion of retrospective studies and studies with the QOL as a secondary outcome in the Cochrane review limit the conclusions of it. A Dutch, prospective, randomised controlled trial in women undergoing laparoscopic hysterectomy or abdominal hysterectomy address the limitations of the Cochrane review. It describes the QOL as the primary outcome of the study. The Short Form Health Survey (Dutch-version) was used.⁽³⁶⁾ Inclusion criteria were benign disease and women in whom a vaginal hysterectomy was not possible. Exclusion criterion was a uterus size larger than 18 weeks. Laparoscopic hysterectomy was associated with statistically longer operating (laparoscopic hysterectomy=116 min vs. abdominal hysterectomy = 77 min) but superior to abdominal hysterectomy in the secondary outcome measures of hospital stay, use of analgesics and convalescence. The study reports a statistically significant better QOL in the laparoscopic hysterectomy group for a period up to four years postoperatively.⁽¹⁸⁾ The Cochrane review and the Dutch study concludes that the laparoscopic hysterectomy, for benign disease, resulted in greater short-term and long-term QOL. This conclusion can be extrapolated to hysterectomy for an early-stage cervical cancer, but prospective data in this regard is lacking.

2.2.2 Radical hysterectomy and trachelectomy

Radical trachelectomy offers fertility preservation in young women with early-stage cervical cancer. The procedure results in a 70% conception rate with a first-trimester pregnancy loss of 10- 21%. This pregnancy loss rate is comparable to the general population. Second-trimester pregnancy loss is increased to 9-10% with the corresponding figure of 3% in the general population. A prospective comparative study over two years of women undergoing radical hysterectomy or radical trachelectomy reports no difference in the QOL between the two groups. Both groups experience significant preoperative depression, emotional distress, and sexual dysfunction when compared to the general population. Improvement of depression and sexual function occurred with follow-up but remained below the norm of the population. Fertility preservation radical trachelectomy does not confirm the improved QOL in comparison to radical hysterectomy.⁽¹⁹⁾ Radical hysterectomy and lymph node dissection is the treatment of choice for localised cervical cancer. Despite high cure rates being reported, significant postoperative morbidity occurs with the procedure. The postoperative morbidity related to bladder, bowel and sexual dysfunction is the result of the disruption of the pelvic autonomic system. Loss of the sympathetic innervation of the bladder may lead to urinary incontinence while parasympathetic denervation may result in retention. Concomitant bowel dysfunction of incontinence and constipation may occur. Parasympathetic disruption may lead to decrease vascular congestion of the vulva and vagina occurring during sexual arousal. Objective tests used to document these organ dysfunctions are urodynamic studies, anal manometer and vaginal photoplethysmographic measurement of vaginal pulse amplitude during sexual stimulation.⁽²⁰⁻²³⁾ Post-operative urodynamic studies report objective bladder dysfunction occurring in 25-30% of patients for up to 12 months after radical hysterectomy. These findings document partial parasympathetic dysfunction with reduced detrusor activity during the filling phase with the resultant decrease in contractility during the voiding phase. Anal manometry

studies directly postoperatively objectively document lower resting and squeeze pressure of the internal anal sphincter in comparison to pre-operative measurements. Pudendal nerve studies reveal conduction impairment up to six months postoperatively. The objective anal manometric abnormalities did not result in impaired QOL. Conversely to these objective abnormalities patients reported an improvement in overall QOL as reflected by pre-and post- operative completion of Functional Assessment of Cancer Treatment-General questionnaires in this study.⁽²²⁾ Objective documentation of anorectal dysfunction, therefore, does not translate into decreased QOL. Objective assessment of sexual dysfunction after radical hysterectomy is done with a photoplethysmographic assessment of vaginal pulse amplitude during sexual stimulation. This method measures the changes in blood flow to the vagina during sexual arousal. The increase in blood flow is related to vasodilation. A Dutch study compares the vaginal pulse amplitude in a control group of healthy women (n=17) with women after a simple hysterectomy (n=12) and in women after radical hysterectomy (n=12). The radical hysterectomy group has a significantly lower maximum response than healthy controls. There is no statistical difference between the abdominal hysterectomy group and the other two groups.⁽²¹⁾ The study did not assess the impact these findings on the QOL of the women.

2.2.3 Nerves sparing radical hysterectomy

Radical hysterectomy with pelvic and para-aortic lymph node dissection results in morbidity due to surgical damage to the autonomic nervous system with resultant bladder or bowel and sexual dysfunction. Surgical techniques aim to minimise nerve damage. Okabayashi in 1944 suggested that the preservation of nerve function would be an important challenge in the future development of radical hysterectomy techniques. Kobayashi in 1961 modified Okabayashi's technique to improve post-operative bladder function. He emphasised preservation of the pelvic splanchnic nerves. In a further development in 1983, Fujiwara illustrated the importance

of preservation of the bladder branch of the inferior hypogastric plexus as well as the pelvic splanchnic nerve preservation to prevent bladder dysfunction. ⁽²⁴⁻²⁶⁾

223.1 QOL and nerve-sparing radical hysterectomy

A longitudinal ten-year cohort study of 229 women undergoing a nerve-sparing radical hysterectomy (n=123) or radical hysterectomy (n=106) reported on QOL-related to the bladder, bowel and sexual function. Women completed the Dutch Leiden Gynaecological questionnaire preoperatively and at one and two years after treatment. The total study group of nerve-sparing radical hysterectomy and radical hysterectomy shows deterioration of bowel, bladder and sexual function at both 12 and 24 months post-operative. There was no statistically significant difference in the QOL-related to bowel, bladder or sexual function between the two groups. Despite a decrease in sexual QOL, in the total group, there was a significant increase in women being sexually active after completion of therapy in the total study group. A total of 58% women were sexually active before treatment and 81% post-treatment. In this study, nerve sparing techniques did not result in a better QOL than the radical hysterectomy.⁽²⁷⁾ Further Dutch study reports on vaginal pulse amplitude in a comparative study of women who underwent nerve-sparing radical hysterectomy and radical hysterectomy. The study documents better vaginal blood flow in the nerve-sparing radical hysterectomy group than radical hysterectomy group. Both nerve-sparing radical hysterectomy and radical hysterectomy groups completed the Dutch version of Female Sexual Function Index. No statistically significant differences occurred in sexual function between the two groups as reflected by Female Sexual Function Index scores. This study concludes that, despite objective vaginal pulse amplitude differences between nerve-sparing radical hysterectomy and a radical hysterectomy, these differences did not impact on different sexual QOL.⁽²¹⁾ In an observational Italian cross-sectional study of 127 patients, no significant difference in bowel-related change on the QOL

and sexually related QOL could be documented between women undergoing a radical hysterectomy (Type II) and nerve-sparing type III hysterectomy. The study used the cervical specific Functional Assessment of Cancer Treatment-Cervix questionnaire. ⁽²⁸⁾

From the aforementioned studies, nerve-sparing radical hysterectomy offers a technique to reduce the damage of the pelvic autonomic nerve system. Evidence exists that the technique reduces objective bladder, bowel and sexual dysfunction. Despite this objective evidence of organ dysfunction, the patient's experience of QOL undergoing radical hysterectomy or nerve-sparing radical hysterectomy, does not differ.

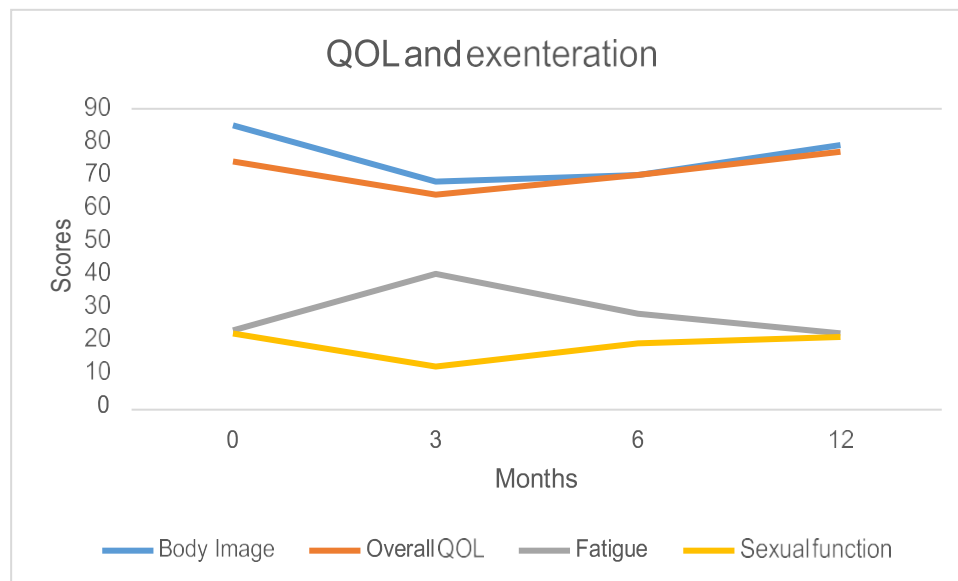
2.2.4 Exenteration

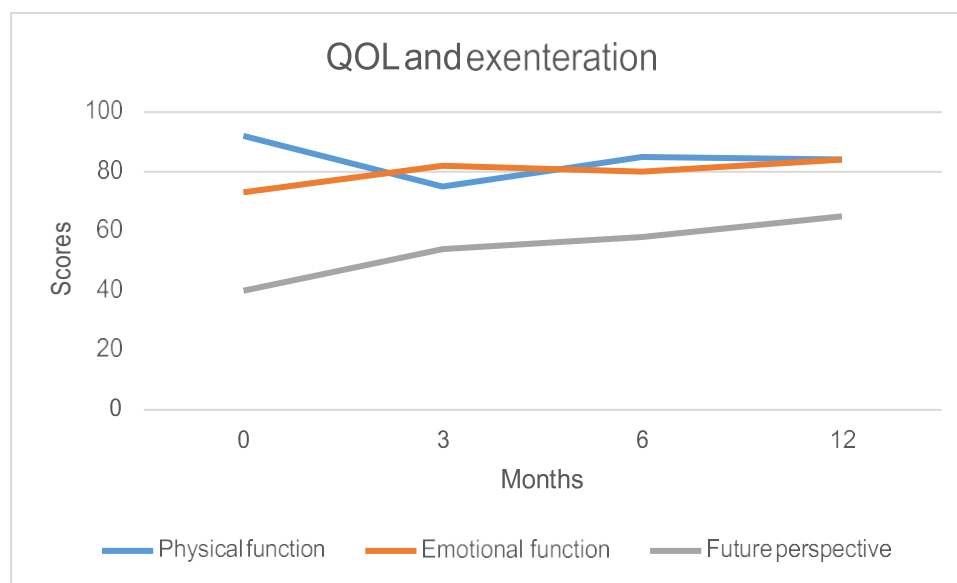
Pelvic exenteration, as reported by Brunswick, involves en bloc resection of the pelvic organs. It is a potentially curative treatment for advanced or recurrent gynaecological cancers. The procedure involves either anterior resection of the bladder uterus and vagina with a urinary diversion or posterior exenteration with resection of the rectosigmoid colon, uterus and vagina with a colostomy. Total exenteration result in double ostomies after en bloc resection of the rectosigmoid colon, uterus vagina and bladder. Reconstruction of the vagina is done with a bowel or skin flaps. Despite the procedure being potentially curative, it has a high operative morbidity resulting in 25% cases having to undergo subsequent surgery after initial exenteration. A study spanning 45 years reports a 50% five-year survival after exenteration. ⁽²⁹⁾ Retrospective studies on QOL after exenteration are of limited value as it relies on patient recall of symptoms. A further limiting factor of these studies is the use of invalidated questionnaires. ⁽³⁰⁾ This results in inaccuracy in the final analysis of QOL. In a prospective study of 62 patients undergoing exenteration for recurrent cervical cancer, a poorer pre-operative QOL in the domains of physical, psychosocial and sexual function and global QOL health

occurred. The exenteration group was compared to patients scheduled for radical hysterectomy.⁽³¹⁾ The psychological impact of recurrence and concomitant negative prognostic implications adversely affects the QOL of women scheduled for exenteration. Postoperatively, the exenteration group, at four months, shows a decline of QOL in the physical domain, sexual domain and the global QOL. The decline of QOL in the sexual domain extends to 12 months. The decreasing sexual QOL is related to the loss of vaginal function. The decrease in sexual QOL and decreasing body image are major contributors to the decreased global QOL after exenteration. The study documents a significant decrease in body image in women with two ostomies subsequent exenteration. Sexual dysfunction after exenteration may be obviated by reconstruction. Vaginal reconstruction is an important psychological aspect as illustrated by the fact that less than 50% of women with a functional reconstructive vagina endeavoured into penetrative intercourse. Despite this vaginal reconstruction significantly improve sexuality and self-esteem.⁽³²⁾ Eight gynaecological oncology unit in the United States of America performed a prospective study on QOL in patients undergoing exenteration. The accrual of only 36 women over an eight-year study period illustrates the rarity of the procedure. Patient filled in a battery of questionnaires preoperative and at three, six and 12 months post-operative visits. The questionnaires include the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30, EORTC QLQ-C38 (colorectal cancer module), EORTC QLQ-BLM30 (muscle invasion bladder cancer module) and Brief Fatigue Inventory. Due to loss of follow-up and death of disease 16 women completed questionnaires at all four occasions. The statistical decrease occurred at three months in overall QOL, physical functioning and sexual functioning. These changes returned to baseline at 12 months. An initial increase in fatigue at three months return to pre exenteration levels at 12 months. Emotional functioning and future perspective increased with time. The limitations of the study included small numbers of women and the analysis of multiple outcomes on these small numbers. Exenteration offers a curative

option in patients with recurrent disease. The progressive increase of QOL in the domains of emotional functioning and future perspective documents increase the QOL subsequently to the procedure. The initial increase in QOL must be weighed against the initial decrease in overall QOL and sexual functioning. The results of the various QOL domains are reflected in graphs 5, 6.⁽³³⁾

Graph 5. The QOL and exenteration using EORTC QLQ-CR38 and QLQ-C30 (33).



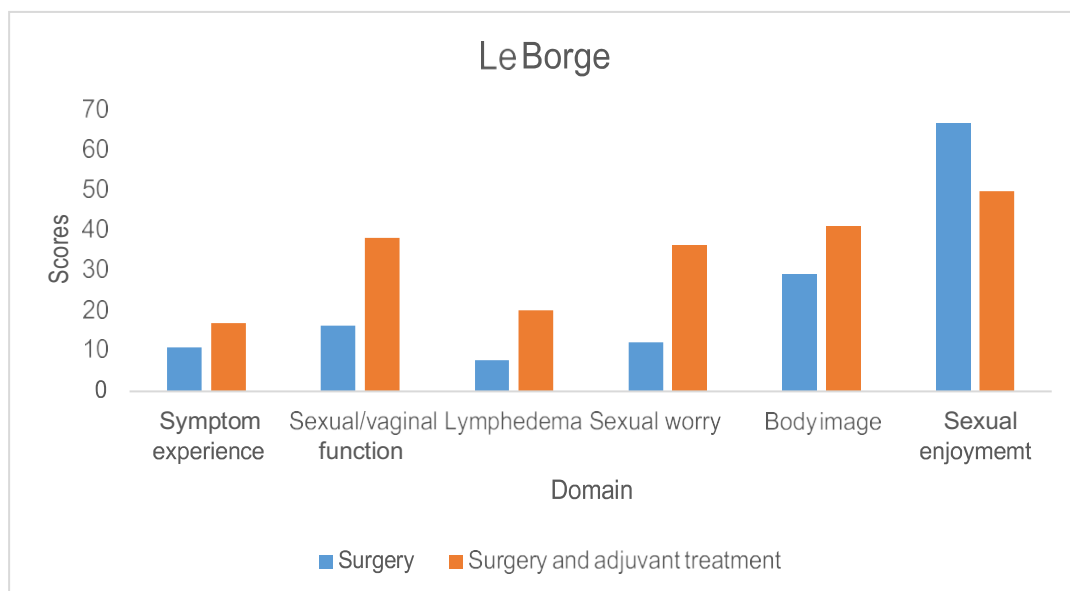
Graph 6. QOL and exenteration using EORTC QLQ-C30 and QLQ-BLM30 (33)

2.2.5 QOL and radiation therapy

Pelvic radiation therapy resulted in damage to normal tissue results and in organ dysfunction of the bowel, bladder and vagina. The mechanism of radiation associated to tissue damage results in acute reaction and long-term consequences. Assessment of the impact of QOL with long-term follow-up will reflect the eventual impact on QOL. A comparative, prospective study objectively assessed bladder dysfunction with a urodynamic measurement three years after radical hysterectomy or chemo radiation in patients with cervical cancer. The study concludes that the radical hysterectomy results in significantly higher voiding dysfunction. Chemo radiation results in storage dysfunction of the bladder. Autonomic nerve damage accounts for the dysfunction in the radical hysterectomy group while predominant radiation-induced fibrosis accounts for the decrease bladder compliance and impediment of storage function in the chemo radiation group. Patients in both chemo radiation and radical hysterectomy groups completed the Thai versions of Urogenital Distress Inventory and Incontinence Impact Questionnaire to assess the QOL. Objective evidence of bladder dysfunction did not affect the QOL in either group.⁽²⁰⁾ Anal manometry documented long-term recto anal dysfunction due to radiation therapy. In a study of patients with late radiation-induced proctitis anal manometry

documented 75% of patients with the objective dysfunction in comparison to 24 healthy controls. Objective sensory and motor dysfunction with the decrease rectal compliance and radiation damage to the external anal sphincter were documented. Due to small numbers of women in the radiation groups QOL analysis could not perform.⁽²²⁾ A French cross-sectional population-based study compared the QOL of 173 cervical cancer patients 5-15 years after diagnosis with 594 healthy controls. At five and ten years follow-up no differences in QOL were observed between controls and patients. At 15 years, differences occurred, with reduced QOL in the domains of global QOL, mental fatigue and more anxiety in cervical cancer patients. Comparing surgery with surgery and adjuvant radiation therapy a statistically significant decrease occurred in the QOL in the latter group at 15 years. Patients who underwent surgery with adjuvant radiation therapy had worse QOL with specific reference to the domains of symptom experience sexual function, sexual worry, body image and sexual enjoyment in comparison the group who underwent surgery alone as shown in Graph 7.⁽³⁴⁾

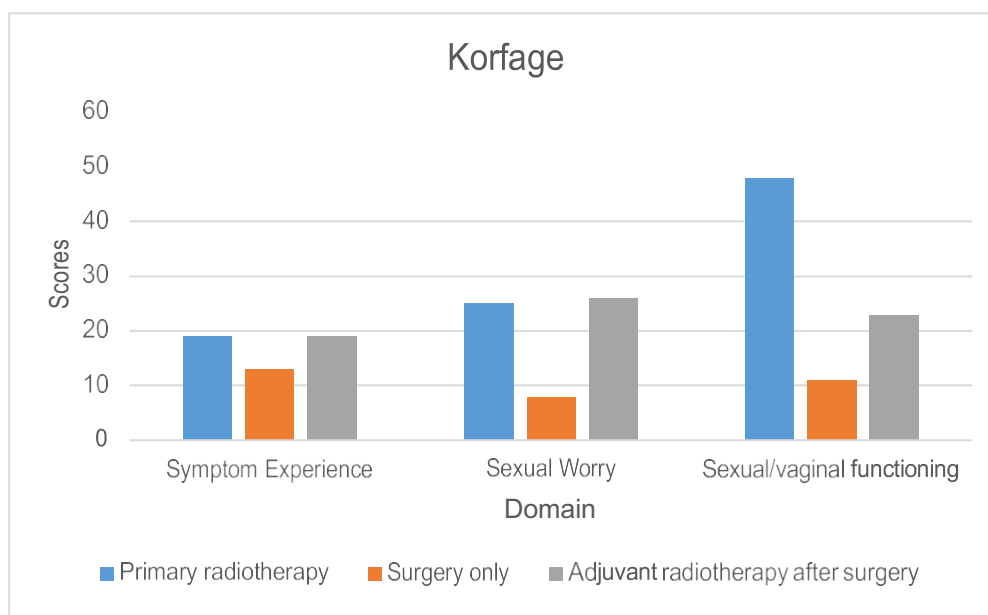
Graph 7. QOL domains 15 years after diagnosis.⁽³⁴⁾



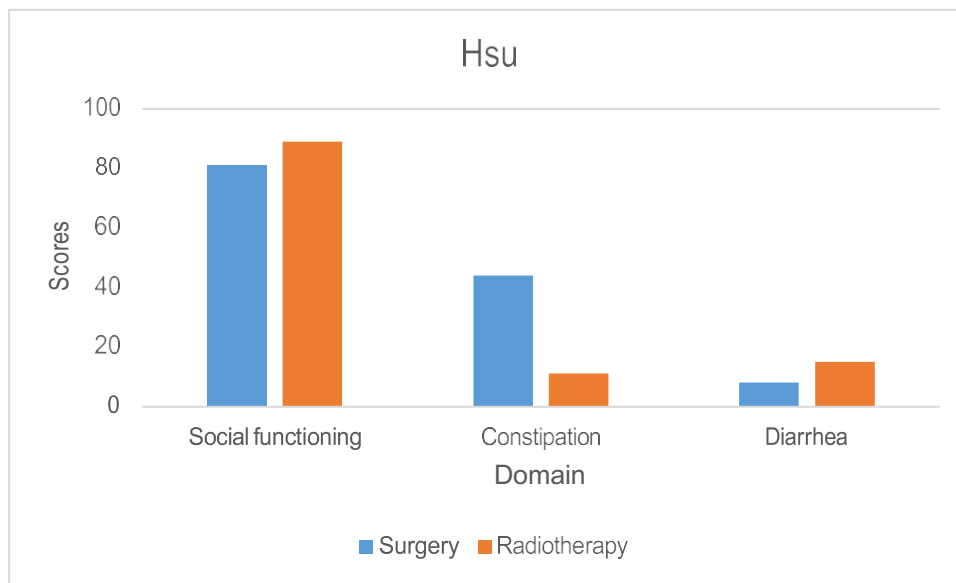
A study on a population-based sample of 291 women with cervical cancer compared the QOL of the various treatment modalities of surgery, radiotherapy and adjuvant radiotherapy after surgery. The generic QOL as reflected by the EORTC QLQ-C 30 scores were equivalent in all

the treatment groups. Cervical cancer-specific QOL, as reflected by EORTC QLQ-CX24, domains of symptom experience, sexual worry, sexual and vaginal functioning were worse off after primary radiotherapy than adjuvant radiotherapy. A significant increase in sexual dysfunction with declining QOL is reported in women undergoing radiation therapy in comparison to women undergoing surgery (Graph 8).⁽³⁵⁾

QOL Graph 8. Cervical cancer-specific QOL as reflected by EORTC QLQ-CX24 scores.⁽³⁵⁾



A comparative analysis of QOL in 202 women with stage IB and IIA cervical cancer treated by surgery or radiotherapy documented statistically significant better social functioning in the radiotherapy group with worse diarrhoea in the radiotherapy group and worse constipation in the surgical group. These findings confirm similar results by Korean study of 860 women (Graph 9).⁽³⁶⁾

QOL Graph 9. Comparative analysis of QOL between surgery and radiotherapy.⁽³⁶⁾

In conclusion, primary or adjuvant radiotherapy results in decreased QOL-related to sexual function. Bladder-related QOL after chemo radiation was similar to women treated with radical hysterectomy. Objective bowel dysfunction occurs after radiotherapy but due to small numbers in studies on QOL of these aspects is inconclusive.

2.2.6 QOL and chemotherapy

Chemotherapy is used in patients with stage IVB disease or recurrent disease who are not candidates for radiation therapy or exenteration surgery. The median survival of this group is less than six months and fewer than 20% surviving beyond a year. Although the improvement of survival is desirable, palliative treatment aimed to improve the QOL by relief of distressing symptoms and psychosocial problems is a realistic therapeutic goal. Several chemotherapy regimens demonstrate response rates. The combination of cisplatin and topotecan (CT) significantly improves survival without reducing the QOL of the women. The Gynaecological Oncology Group 179 study is a phase III study of recurrent or advanced cervical cancer. The patients were randomised between CT and monotherapy cisplatin. The median progression-free survival in the CT group was 4.6 months versus 2.9 months in the cisplatin group. Despite significant haematological events (neutropenia, febrile neutropenia and thrombocytopenia) in

the CT combination therapy group, QOL did not differ in the CT group and cisplatin monotherapy group. The mean Functional Assessment of Cancer Treatment-General score at nine months after randomisation was 74.4 in CT group compared with 74.5 the cisplatin monotherapy group. Chemotherapy, therefore, offers moderate survival benefits, and potential side-effects and impact on QOL should be considered prior to initiating chemotherapy.⁽³⁷⁾

2.3 Comorbidities

2.3.1 Medical diseases

An Italian study identified diabetes (39%) and connective tissue disease (17, 1%) as the two most frequent comorbid conditions in locally advanced cervical cancer (stages IB2-IVA). The mean age of this study group was 52.5 years. The study concluded that neither overall survival nor disease-free survival of patients was affected by the presence of comorbid disease.⁽³⁸⁾ A Korean study documents increased comorbid conditions in cervical cancer survivors 7.3 years after completion of treatment. Compared to the control group of the population cervical cancer survivors had significantly more heart disease, liver disease, hypertension, gastrointestinal disease and musculoskeletal disorder. Cervical cancer survivors had a mean age of 56 years compared to the control group of the general population with a mean age of 42.5 years. This age difference may account for the high incidence of comorbid disease e.g. heart disease and hypertension in cervical cancer survivors. High incidence of liver disease in cervical cancer survivors could be related to unsafe sexual practice with a resultant risk factor for hepatitis B infection. Hepatitis B infection is endemic in Korea. The presence of comorbid disease had a significant impact on QOL of cervical cancer survivors. A statistically significant decrease in QOL occurred in patients with heart and renal disease. The EORTC QLQ-C 30 and CX 24 questionnaires shown a meaningful decrease in the domains of global quality-of-life, role function, social function, dyspnoea, constipation, body image and lymphedema in a woman with heart disease. The renal disease resulted in significantly lower social functioning, more

financial difficulties, poorer body image, more sexual worry, poorer sexual function and more lymphedema. Cerebrovascular disease is associated with increased pain and poorer sexual function. Diabetes resulted in more sexual worrying, a lung disease with more dyspnoea and musculoskeletal disease with more peripheral neuropathy. Liver disease, hypertension and gastrointestinal disease catching had no effect on the QOL.⁽³⁹⁾

2.3.2 Acquired immunodeficiency syndrome and QOL (AIDS and QOL)

Cervical cancer is an AIDS-defining condition, as determined by the Centres for Disease Control and Prevention. The World Health Organisation designate cervical cancer as stage IV disease in their clinical staging of acquired immune deficiency syndrome. HIV-positive women with cervical cancer have a poor prognosis when compared to their HIV-negative counterparts. The poor prognosis is because HIV -positive women present a more advanced stage disease and have a less chance of completing treatment than HIV-negative women. Low CD4 counts limit chemoradiation's administration.⁽⁴⁰⁾ Demographic data from studies of AIDS and cervical cancer in South Africa consistently demonstrated a younger age of HIV-positive cervical cancer cases. A consistent mean age of 41 to 44 years of HIV -positive cases are reported in these studies. Simmons recorded a statistically significant higher percentage of advanced stage cervical cancer presentation in HIV-positive cases Moodley, and Lomalisa displayed a lack of statistically significant difference in stage distribution.

Table 6. South African studies on cervical carcinoma in Human Immunodeficiency Virus (HIV) + patients.
* = Statistically significant.

Author	N	HIV+ (%)	Mean age(years)		Stage III and IV (%)	
			HIV-	HIV+	HIV-	HIV+
Lomalisa(41)	836	7,2	53*	44*	55	65
Moodley(42)	271	21,8	54*	41*	94	64
Simonds(40)	383	18,2	50*	41*	58*	65*

The QOL of patients with AIDS and cervical cancer is not well studied. A recent study documented that AIDS did not adversely influence the QOL in newly diagnosed cases of cervical cancer when compared to human immunodeficiency virus-negative cases.⁽⁴³⁾ Studies on the QOL of patients with AIDS and cervical cancer, subsequent to treatment with follow-up, are lacking.

2.4 Conclusions: Medical factors and QOL in cervical cancer

Age has an important influence on the QOL of women with cervical cancer. Normal age-related changes in QOL serve as background reference values. These age-related changes are culture and country-specific. Stage of cervical cancer at diagnosis impact on the physical domains of QOL due to the present symptoms. Mental components of QOL are unaffected by stage. Treatment, as determined by stage, has a significant impact on QOL. Pre-existing depression has an adverse effect on women diagnosed with abnormal cytology. Laparoscopic hysterectomy confers a better short and long-term QOL in women undergoing hysterectomy for benign disease. Corresponding figures for simple hysterectomy in early-stage cervical cancer are lacking. Fertility-sparing radical trachelectomy does not result in better QOL than

radical hysterectomy. Nerve-sparing radical hysterectomy results in an objective decrease in the bladder, bowel and sexual dysfunction in comparison to radical hysterectomy. These objective decrease does not result in better QOL than radical hysterectomy. An exenteration is a curative option with the differential effect on various domains of QOL. Sexual QOL is severely compromised, and vaginal reconstruction may obviate this. Emotional functioning and future perspective are statistically improved with exenteration. Chemo radiation does not adversely affect bladder related QOL domains in comparison to radical hysterectomy. Evidence of objective bowel dysfunction after radiotherapy exists. The effect on the QOL is unknown. Radiotherapy results in a statistically significant decrease in the sexual domains of QOL for an extended period of up to 15 years post-treatment. Advanced and recurrent cervical cancer cases are amenable to combination CT chemotherapy with limited improved survival and no decrease in QOL. Comorbid disease, e.g. diabetes, is prevalent in cervical cancer survivors. Various domains of QOL are influenced by medical disorders. AIDS does not adversely influence the QOL in newly diagnosed cases of cervical cancer.

Table 3: Results of Cochrane meta-analysis of surgical approach to hysterectomy for benign gynaecological disease: Comparative outcomes with abdominal hysterectomy (AH), laparoscopic hysterectomy (LH), and vaginal hysterectomy, laparoscopic-assisted vaginal hysterectomy (LAVH) and total laparoscopic hysterectomy (TLH). *Statistically significant, †statistically non-significant, ‡ Mean difference, § Odds ratio, || Confidence interval ⁽¹⁹⁾

	time	operative		88	activities		
		visceral					
		injury					
VH vs AH	ss* Opposing directions.	ns†	ns†	VH less OR§ = 0.42, 95% CI 0.21 to 0.83.	VH shorter MD 1.1 days.	VH sooner MD‡ 9.5 days.	VH better
LH vs AH	AH shorter MD‡ 11.8 minutes.	ns†	ns†	LH less infections OR§ =0.31, 95% CI 0.12 to 0.77. LH fewer febrile episodes OR§ =0.67, 95%CI 0.51 to 0.88.	LH shorter MD 2.0 days.	LH sooner MD‡ 13.6 days.	LH better

LAVH vs TLH	LAVH shorter MD‡ 23.3 minutes.	ns†		ns†		
LH vs VH	VH shorter MD‡ 39.3 minutes.	ns†	LH more OR§= 2.76, 95% CI 1.02 to 7.42	ns†	ns†	LH better

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Chapter 3. Quality of life and contextual factors

3 Introduction

The non-medical contextual factors that influence the QOL of cervical cancer patients include race, socioeconomic status and personal factors e.g. religion and marital status. The influence of the various factors will be described in this chapter and literature will be used to illustrate specific results.

3.1 Race

3.1.1 Definitions of the race, ethnicity and nationality

The United Nations Statistical Division reports 63% of countries incorporate some form of ethnic enumeration in national censuses. Enumerations are used as a form of political control or monitoring of non-discrimination or may form the national discourse of hybridisation. Hybridization is a crossing and or mixing between two separate races or cultures. In the United Nations study, the formatting questions with regards to race/ethnicity included in censuses varied considerably. A diverse conceptualisation of ethnicity occurred in terms of race and ethnicity and nationality used interchangeably between countries.⁽¹⁾ The definition of an ethnic group is a connectivity within a larger population having real or punitive common ancestry, and memories of a shared past and cultural that focus upon one or more symbolic elements which define the group identity such as kinship religion, a language shared territory, nationality or physical appearance.⁽²⁾ Racial classification revolves around physical and biological commonality traits. These traits are inheritable or non-inheritable and demonstrate common descent.^(3,4) Nationality refers to the country or region of birth. In medical research, the terms of race-ethnicity and nationality are ill-defined. In particular contexts, the exact meaning is revealed. An example is the higher occurrence of BRCA 1 and two genetic mutations in the Ashkenazi group (ethnic) amongst Jewish people (nationality). The United Nations recommends that all individuals must be left free to self-identify themselves and to declare or

non-declare race and ethnicity. Self-identification has the disadvantage of people who want to avail themselves of an advantage accorded to protected groups but are not themselves affected by the inequalities and discrimination that those groups suffer.⁽¹⁾ Race and ethnicity are social constructs formed in the discipline of sociology. The use of these terms in medical research represents a transdisciplinary approach and is essential in addressing specific cancer-related issues e.g. racial disparities in cancer incidence, treatment and outcome.

Attempts to categorize and conceptualize race and ethnicity reveals the terms to be complex and multidimensional constructs within in a geopolitical context. In an attempt to clarify the issues Ford and Kelly use the background of the Veterans affairs population in the United State of America.⁽⁵⁾ They proceed to quote Jones to justify “*new taxonomy for racial identification*” and propose the classification rather be “racism” (instead of race) to define the inherent qualities of the patient’s immediate and broader environments. They conclude that it is imperative that health researchers find more accurate ways to measure race and ethnicity.⁽⁶⁾

3.1.2 QOL differences of ethnic/racial groups and nationalities without cancer

Sociology defines the uniqueness of ethnic and racial group in terms of commonality of value systems and beliefs amongst individuals. Inherent in this sociological construct are the differences in beliefs and value systems between various ethnic groups. These differences express themselves in various aspects of life e.g. moral philosophy, political convictions, and religious and secular value systems. Ethnicity influences the QOL due to the priorities allocated by a particular group to various domains of physical and mental well-being.

The EORTC QLQ group used the questionnaire to identify cultural differences in response to the EORTC-QLQ-C 30. The study included 106 datasets incorporating data from 289333 respondents. The analysis was adjusted by correcting for confounding variables of age, gender, cancer site and stage of the disease. The study defined culture using geographical areas (Table

1) ⁽⁷⁾

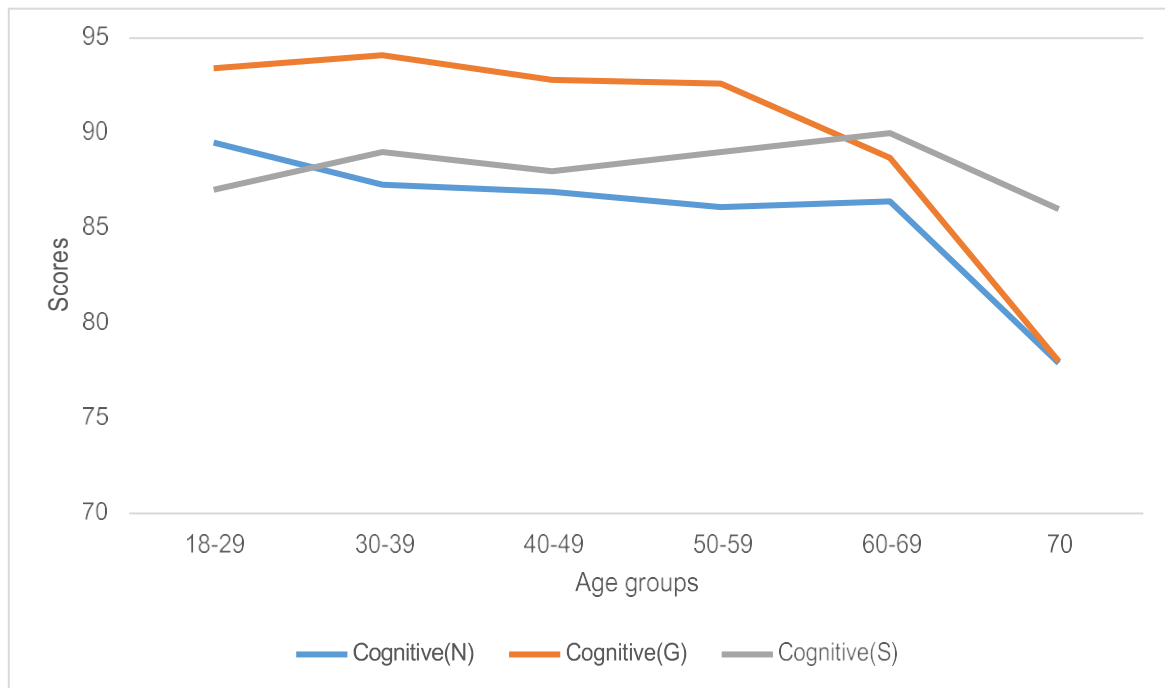
Table 1. Cultural groupings according to geographic regions used in differential item functioning assessment to determine ethnic differences in response to EORTC-QLQ-C30 in healthy populations. ⁽⁷⁾

Scandinavia	North Central Europe	South West Europe	Eastern Europe	Islamic countries	East Asia	North America
Norway	Germany	France	Poland	Turkey	South Korea	USA
Sweden	Netherlands	Spain	Russia	Iran	Singapore	Canada
Denmark	Austria	Italy	Hungary	Egypt	Taiwan	
	Belgium	Belgium			China	
	Switzerland				Myanmar	
					Singapore	
					Hong Kong	

The United Kingdom version of the questionnaire was chosen as the reference group as the EORTC-QLQ-C30 was initially developed in the English language. Linguistic sub-analysis by differential item functioning was done in multilingual countries. The result of the study reported similar response in the various languages to questionnaires in Dutch-speaking countries (Netherlands and Belgium), Francophone countries (Belgium France and Canada) and German-speaking countries (Germany Austria and Switzerland). A striking variation occurred in the far Eastern European and Asian groups, and these were particularly evident for countries make up the Eastern Asian block. The Singaporean sample was bilingual, and the patients had a choice of the English or Chinese translation of EORTC QLQ-C30. A number of

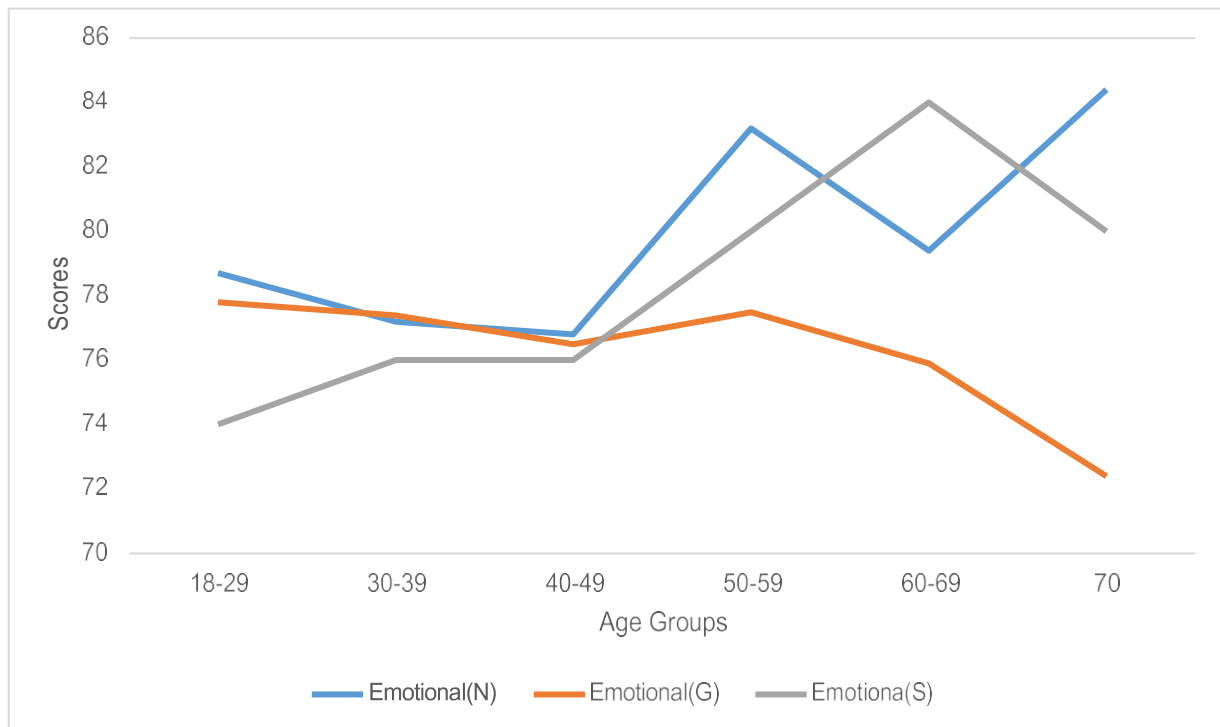
scales resulted in the English version of the Singaporean responses appeared closer to those of the Chinese in East Asian countries than the English-speaking countries. This finding illustrates that the DIF was primary of cultural rather than the linguistic origin. The response in Europe was based upon linguistic lines. The Asian participants scored higher on all emotional items in comparison to their European counterparts. The study concludes that cultural differences exist in response to the EORTC-QLQ-C30 questionnaire. Translation, linguistic causes, is not a plausible explanation for these differences but these differences are related to cultural differences. The disadvantage of the study includes the arbitrary nature of the cultural groupings.⁽⁸⁾ To assess the impact on QOL of cancer, normative values for questionnaires are used. Normative reference values are made by administering the questionnaire to their healthy, normal population. Population reference values for the EORTC-QLQ-C30 is available for Norway, Germany and Sweden in three separate studies.⁽⁹⁻¹¹⁾ These studies stratify normative data for various domains of the EORTC-QLQ-C30 according to age groups. By combining the results of these studies is, it is evident that population-based differences exist in the QOL experiences. In the domains of cognitive and role functioning, clear differences exist between the different nationalities. The cognitive domain of QOL in the Swedish population remains constant with age. This finding is in comparison to the decline in the Norwegian and German nationalities (Graph 4).

Graph 4. The combination of values for the EORTC-QLQ-C30's cognitive domain scores in the healthy Norwegian, Swedish and German female population.⁽⁹⁻¹¹⁾



The age-related decline in the emotional functioning occurs the German population. The Swedish and Norwegian show an increase in the same domain with age (Graph 5).

Graph 5. The combination of values for the EORTC-QLQ-C30's emotional domain scores in the healthy Norwegian, Swedish and German female population.⁽⁹⁻¹¹⁾



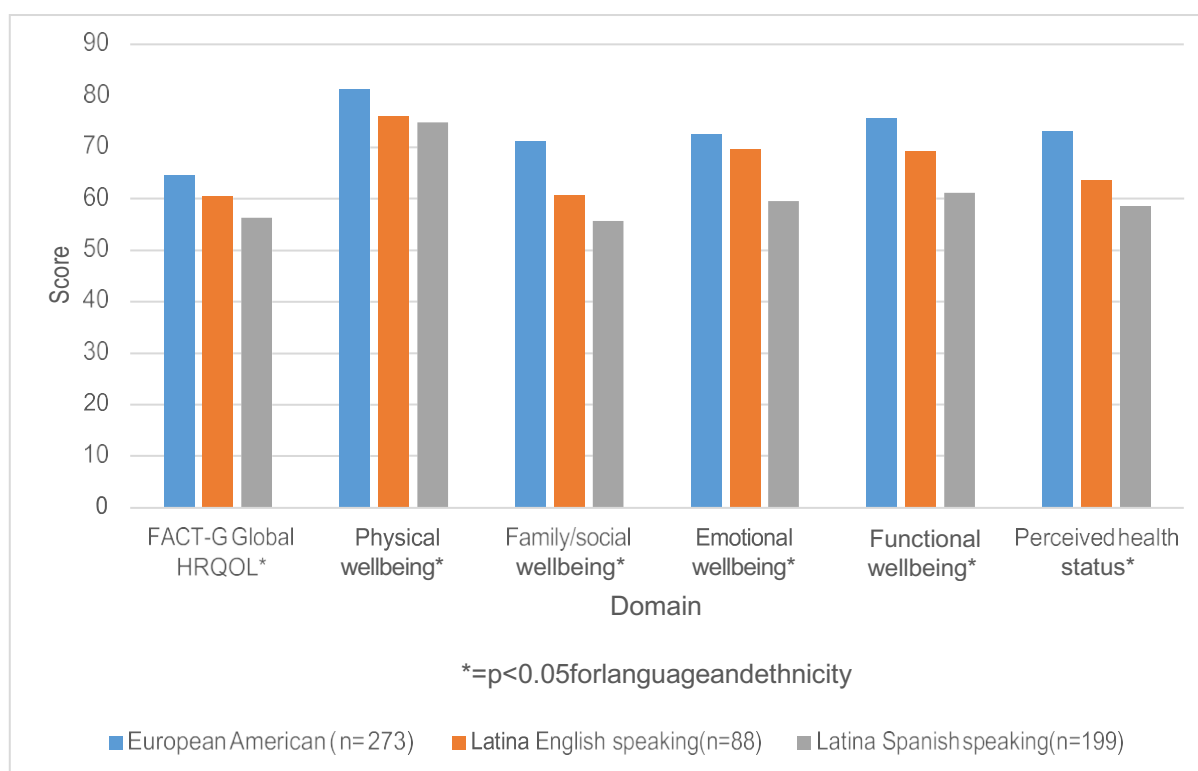
Normative reference values for the EORTC QLQ-C30 document differences between nationalities sharing a geographic region. In conclusion, QOL scores vary according to nationalities and within nationalities along cultural, ethnic/racial and linguistic groupings.

3.1.3 Race/ethnicity, QOL and cervical cancer

An American cross-sectional population-based sample study describes the impact of race and ethnicity on the QOL of the life of patients with cervical cancer. The study includes 560 patients. Inclusion criteria included a time span of one to five years after diagnosis of cancer. The patients were cancer free at the time of completion of the questionnaires. Questionnaires used include the Functional assessment of cancer therapy – Cervix (FACT-CX), (SF-36) and 12-Item Short Form Health Survey (SF-12). Study participants self-identified as European/White or Latina Americans. A total of 273 European-American and 287 Latinas participated. The Latina group was subdivided into participants completing the English questionnaires or the Spanish questionnaires. Stepwise, multiple regression analyses corrected

for confounding variables of socio-economic factors, demographic data, health system factors, current health status, medical/cancer relevant factors and psychological aspects. The final ethnic, linguistic results of the Functional assessment of cancer therapy – Cervix (FACT-CX) appears in Graph 6. Spanish-speaking Latinas had a statistically significant worse QOL in all domains of the Functional assessment of cancer therapy – Cervix (FACT-CX). English-speaking Latinas had a better QOL than Spanish-speaking Latinas. The English-speaking Latinas ability to access health care facilities and experience community-based support was related to the ability to communicate in English. The study concludes that the QOL is significantly influenced by both race/ethnicity and linguistic factors.⁽¹²⁾

Graph 6. The Functional assessment of cancer therapy – Cervix (FACT-CX) scores in European, Latina English speaking and Latina Spanish speaking Americans with cervical cancer.⁽¹²⁾



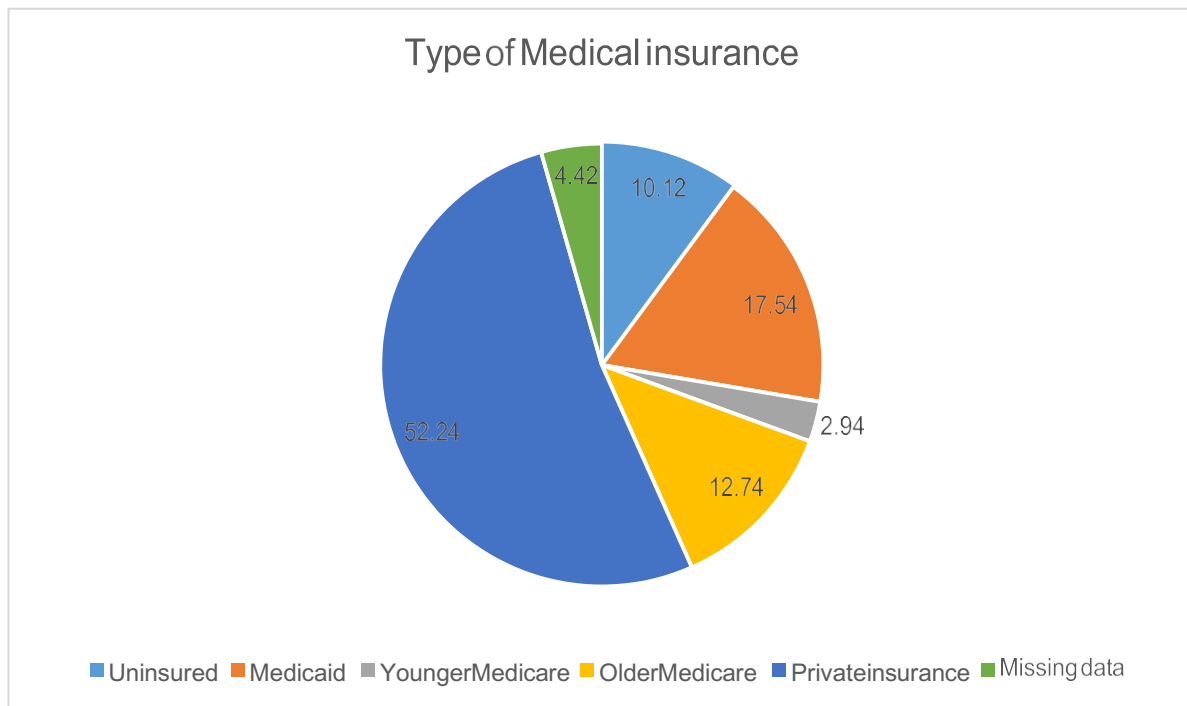
3.2 Socioeconomic status

Socioeconomic status is a measure defining the social standing or class of individuals or groups. It is a combined measurement of education, income and occupation. Examination of socioeconomic status often revealed inequities in access to resources and issues related to privilege power and control.⁽¹³⁾ Socioeconomic status influences the incidence of cervical cancer by its indirect effect on the epidemiological factor of the early age of coitarche and the direct effect of the health system's contribution to the provision and utilisation of cervical cytology screening facilities.

3.2.1 *Advanced cervical cancer and socioeconomic status*

A direct relationship exists between medical insurance status, age and cervical cancer stage at diagnosis. A USA cancer registry-based cohort of 69739 patients with cervical cancer compared the proportion of late-stage disease stage (Stage III/IV) with age and medical insurance status. The medical insurance categories included are Medicaid, Medicare, private insurance and uninsured. Medicaid is a United States of America governmental based insurance program. It serves as insurance for persons of all ages whose income and resources are insufficient to pay for healthcare. It represents the largest source of funding for medical and health-related services for people of low income. Medicaid is a United States of America federal program providing health insurance for Americans above the age of 65 years old who have worked and paid into the system. Also, younger people with disabilities and in end-stage renal failure is covered by this insurance. Graph 7 reflects the insurance status of the study cohort.⁽¹⁴⁾

Graph 7. The types of medical insurance in the United States of America cancer registry-based cohort of 69739 patients with cervical cancer. ⁽¹³⁾

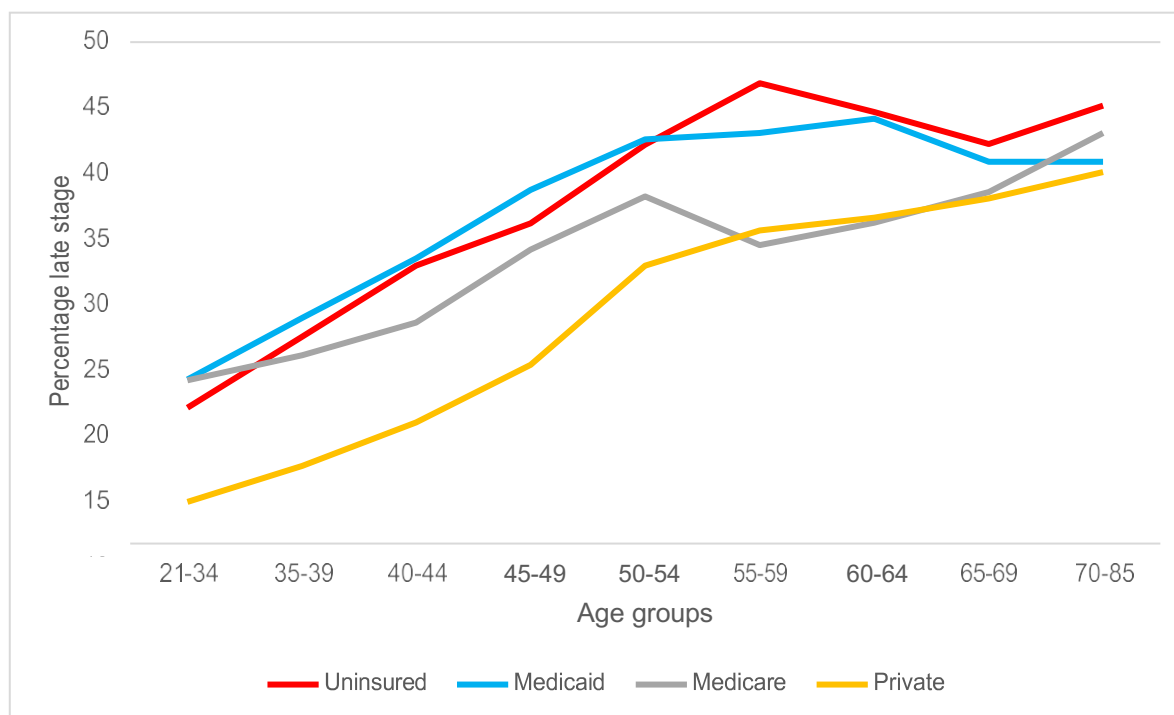


Multivariate models are predicting the advanced stage of cervical cancer identified age and insurance status as the most significant predictors. Graph 8 represents the age-related incidence per insurance category and **Table 2** displays the relative risks of the various groups.

Table 2. The relative risk for advanced stage cervical cancer based on insurance category of the United States of America cancer registry-based cohort of 69739 patients with cervical cancer. ⁽¹³⁾

Category	Relative Risk	95% Confidence interval
Uninsured	1.44	1.40-1.49
Older Medicaid	1.37	1.34-1.41
Young Medicaid	1.12	1.06-1.19
Medicare	1.20	1.15-1.26

Graph 8. The percentage late-stage cervical cancer per insurance category of the United States of America cancer registry-based cohort of 69739 patients with cervical cancer.⁽¹³⁾

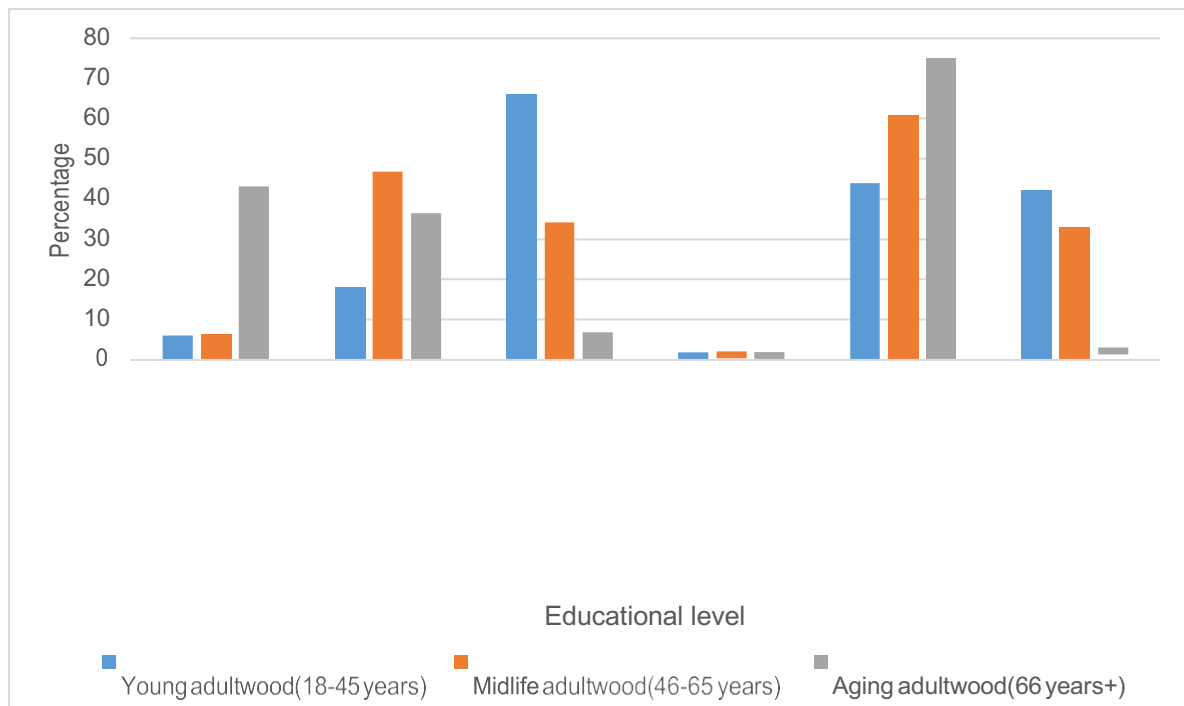


3.2.2 Socioeconomic status and QOL

In a Dutch population-based sample of 291 cervical cancer survivors, the socioeconomic status of the cancer survivors was compared to the general population group. The cervical cancer survivors had a less favourable socioeconomic status with low educational levels, and less often paid jobs in comparison to the reference group.⁽¹⁴⁾ A study of a population-based sample of 560 cervical cancer survivors in the United States of America examined the impact of socioeconomic status on the QOL. The study's primary purpose was to examine the impact of ethnicity and language on the QOL, and the further aim was to identify contextual factors predictive of QOL. The study used the contextual model of QOL. This model includes the social-ecological context, cultural context, the demographic context, healthcare system context, general health and comorbidity, cancer-related medical factors, health efficacy and psychological well-being. These contextual factors were analysed to identify predictors of

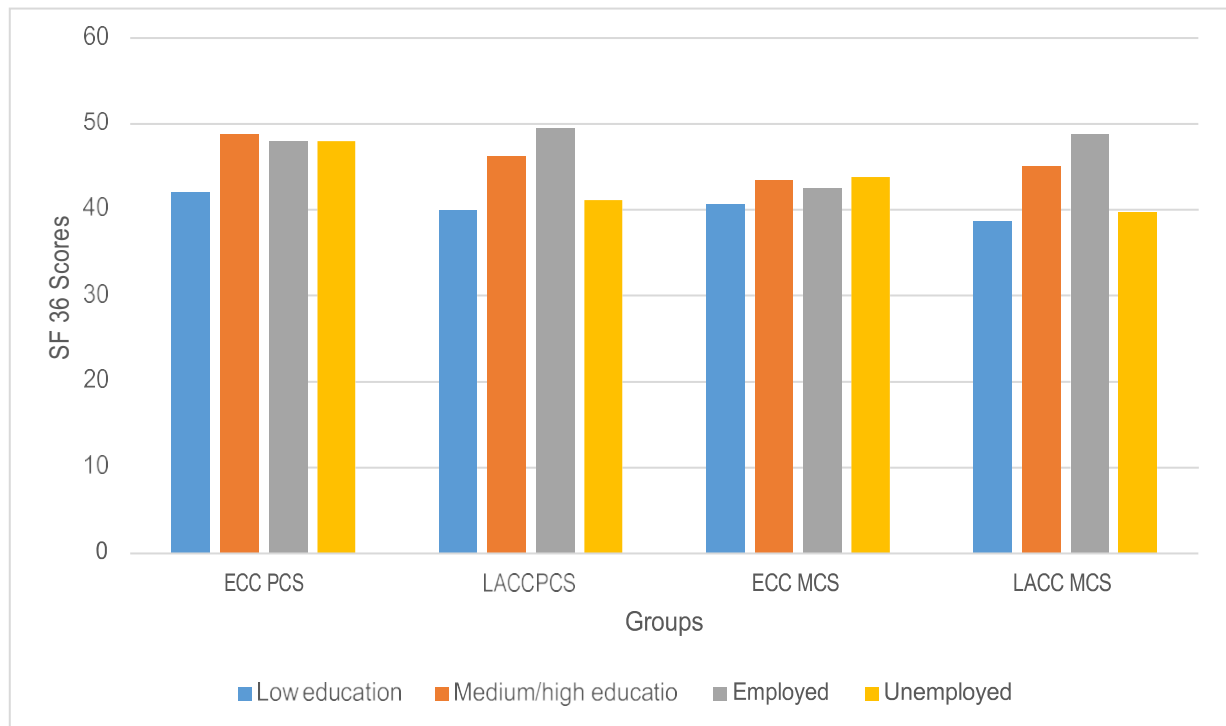
QOL as measured by Functional assessment of cancer therapy – Cervix (FACT-Cx). Socio-ecological factors included socioeconomic status, life stress, and social support. Socioeconomic status was defined in terms of self-reported household income and the highest level of education completed. Life stress was measured by the 19-items Life Stress Scale, and the Medical Outcome Social Support Survey questionnaire was used to assess emotional, informational tangible and affectionate support. Stepwise multiple regression analyses were performed to evaluate the impact of contextual factors on the QOL. Household income did not affect the QOL, but social support was a significant determinant of QOL. Limitations of the study include the mail based accrual of patients with less than 50% responders on the initial invitation letters. The cross-sectional design of the study and the absence of normal, healthy group for comparison are additional limitations. Although the original methods and material section include the level of education as part of the socioeconomic status subcomponent of socio-ecological factors no further data is provided in the results or discussion section on these factors impact on QOL.⁽¹⁵⁾ In a further article by Ashing-Giwa, the same group of 560 cervical cancer survivors are subjected to structural equation model analysis to examine the relationship between QOL and the contextual factors as described in the original paper. In the second paper, social-ecological factors are defined as a life burden and socioeconomic status. Life burden was measured by 14 items of Life Stress Scale. Household income represents socioeconomic status. The study excluded employment status and education “*because they were considered as items of functional stress variables.*” A structural equation model showed poor correlation between Functional assessment of cancer therapy – General (FACT-G) domains and contextual factors. The Functional assessment of cancer therapy – General (FACT-G) domains included physical well-being, social well-being, emotional well-being and the functioning well-being. The corresponding correlation coefficient values were .21, .33, .29 and .38. The study confirms the earlier study that socioeconomic status as reflected by income does not significantly affect

the QOL. This study suffers from the same limitations as the original study.⁽¹¹⁾ The omission of educational levels and employment from the criteria of socioeconomic status as contextual factor limit conclusions between these factors and QOL. A Chinese study of 173 cervical cancer patient's evaluates the QOL and its association with age, level of education, employment status and number of children in the family. The WHOQOL-BREF-HK (World Health Organisation Quality of Health Scale-Chinese Hong Kong version) was used, and multiple regression analyses were used to assess the influence of above listed contextual factors on QOL. Analysis of covariance was performed. Covariance is measured by how much two variables change together when a strong relationship exists between them. It represents a general linear model which blends analysis of variance and multiple regression analyses. The study group was divided according to the age group of young adulthood (18-45 years), midlife adulthood (46-65 years) and ageing adulthood (66+ years). The literacy and employment rates of the study population are reflected in Graph 9. Retirement associated with advanced age resulted in a statistically significant decrease employment rates with age, and the ageing adult group had a statistically significant high rate of illiterates. The patients in the young adult group's QOL were positively associated with employment status and educational level. A higher education level and being employed were associated with better QOL in this age group ($p=0.03$, 0.00). These findings were not present in the midlife and ageing adulthood groups.⁽¹⁶⁾

Graph 9. The education levels per age group of Chinese cervical cancer cases.⁽¹⁷⁾

QOL and psychological distress in cervical cancer patients are the focus of an Italian study of 93 patients 12 months after completion of treatment. In this study, the Hospital Anxiety and Depression Scale (HADS) and the Short Form (36) Health Survey (SF-36) questionnaire was utilised. The Short Form (36) Health Survey (SF-36) is subdivided between a mental component summary (MCS) and physical component summary (PCS). The study population was divided into early-stage cervical cancer patients (ECC) and locally advanced cervical cancer cases (LACC). The early stage cervical cancer patients (ECC) included stage IB-IIA <4cm tumour size. Locally advanced cervical cancer cases (LACC) included stage IB-IIA >4cm tumour size, IIB-IVA. Graph 10 reflects univariate analysis of the effect of educational level and employment status.

Graph 10. Short Form (36) Health Survey (SF 36) scores of the mental component summary (MCS) and physical component summary (PCS) per educational level and employment status of Italian women with early-stage cervical cancer patients (ECC) and locally advanced cervical cancer cases (LACC).⁽¹⁸⁾



In early-stage cervical cancer patients, physical component summary and mental component summary scores were not statistically significantly influenced by educational level or employment status. In locally advanced cervical cancer cases, physical component summary scores and mental component summary scores were statistically significant decreased by unemployment. To assess the impact of disease-related socio-demographic features and treatment-related factors on the QOL, multivariate analysis was performed on the following parameters a) age b) comorbid disease c) treatment type d) marital status e) educational level and f) employment status. Low educational level was statistically significantly associated with a mental component summary and physical component summary scores ($P=0.075$, 0.0089).

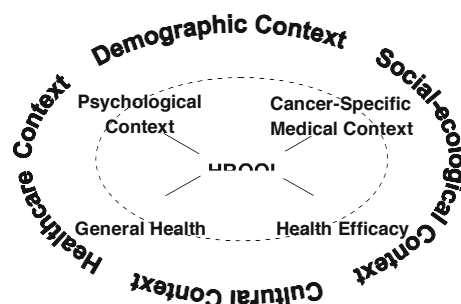
Unemployment did not significantly impact the physical component summary but did impact the mental component summary scores ($P=0.010$).⁽¹⁸⁾

3.3 Religion, marital status and mental health and its effect on QOL

Women report gender-specific changes QOL-related to illness. These differences are illustrating specific mental health conditions a cohort of men and women with similar mental health conditions women had a significantly greater decrease in QOL in comparison to their male counterparts. These differences may be attributable to women's vulnerability and reliance on social support.

Social support improves the QOL of cervical cancer patients. This social support includes social relationships and the presence of life partner. The support of a religious community further contributes to the QOL.⁽¹⁹⁾ In a Chinese study, the midlife adulthood group of patients documented that the religious belief is positively associated with the overall QOL.⁽¹⁷⁾ The presence of a partner had a positive association with higher QOL. In contrast to the Chinese study, marital status did not affect the QOL in Italian cervical cancer cases.⁽¹⁸⁾ Ashing-Giwa uses spirituality as a contextual factor that could impact the QOL. In both multivariate analysis and structured equation modelling of the same group of cervical cancer survivor's spirituality did not significantly impact the QOL.^(11,20) The conclusions of these two studies are limited due to the use of an invalidated instrument to measure spirituality.

Ashing-Giwa developed the Contextual model of health-related QOL to incorporate multiple factors influencing the QOL. This model was developed by quantitative and qualitative outcome research consists of individual and systemic factors. These factors include medical factors, general health status, psychological well-being, socio-ecological factors, health care system, cultural demographic features.⁽²¹⁾ (Figure 1)

Figure 1. The Contextual Model of health-related QOL. ⁽¹⁹⁾

3.4 Conclusions: Contextual factors and QOL

Race/ethnicity influence the race-specific incidence rates of cervical cancer due to difference in age of coitarche and health system factors. Health system factors include race/ethnicity based utilization of existing healthcare facilities and disparities in the availability of facilities. Differences of QOL exist in nationality based healthy population due to differences in belief, and value systems of these different populations. Ethnicity, race and language are linked to certain circumstances. Despite this linkage, race and language has independent effects on QOL. Socioeconomic status influence age of coitarche and therefore the rate of cervical cancer. Availability and utilisation of cervical screening programmes are influenced by the socioeconomic status of individuals and countries. The rate of late-stage cervical cancer is affected by socioeconomic status as reflected by medical insurance categories. QOL is not adversely affected by low income. Higher education and employment lead to improved QOL in young adulthood (18-45 years). Conflicting report exists on the impact of marriage and QOL. Data on the relationship between the contextual factors of race, employment and education level in cervical cancer patients is lacking. The effect of contextual factors on QOL in longitudinal studies is lacking.

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Chapter 4 A prospective study of the QOL of women with cervical cancer undergoing treatment for cervical cancer at Tygerberg Hospital.

This chapter includes a prospective study of the QOL of women with cervical cancer undergoing treatment for cervical cancer at Tygerberg Hospital. The research is presented as an article. The article describes the influence of contextual factors on the various QOL domains.

Du Toit GC, Kidd M. A prospective quality of life study of South African women undergoing treatment for advanced-stage cervical cancer. *Clinical Therapeutics* 2015;37(10):2324-2331.

Prospective Quality of Life Study of South African Women Undergoing Treatment for Advanced-stage Cervical Cancer

George Campbell du Toit, MBChB, MMed, FCOG/LKOG(SA)¹; and Martin Kidd, PhD²

¹Unit of Gynaecological Oncology, Tygerberg Hospital, University of Stellenbosch, Stellenbosch, South Africa; and ²Centre for Statistical Consultation, University of Stellenbosch, Stellenbosch, South Africa

ABSTRACT

Purpose: The majority of South African cervical cancer patients present with advanced-stage disease. Chemoradiation therapy, in comparison with radiation therapy, results in marginally improved survival in women with advanced cervical cancer. The impact on the quality of life due to the addition of a chemosensitizer in a situation of limited survival benefits warrants objective assessment. This prospective study compares the quality of life for women with cervical cancer and treated with radiation or chemoradiation therapy at Tygerberg Hospital, South Africa.

Methods: A prospective study was done in a population with a high incidence of advanced cervical cancer. Quality of life measurements were done at pretreatment, post treatment, and follow-up. The European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire and the Cervix Cancer Module were used.

Findings: The study included 219 women. Forty-four women were treated with primary surgery. A total of 102 women completed primary radiation therapy and 73 women completed primary chemoradiation therapy. The demographic characteristics of the last 2 treatment groups were different. Women receiving chemoradiation therapy had a higher educational level ($P < 0.01$) and had less advanced stage (III or IV) cervical cancer ($P < 0.01$). Radiation therapy was used significantly more in HIV-positive women. The presiding clinicians chose treatment options based on clinical factors unrelated to quality of life. Chemoradiation therapy resulted in statistically more improvement in the pain ($P < 0.05$), fatigue ($P < 0.05$), appetite loss ($P < 0.01$), and nausea and vomiting ($P < 0.05$) quality of life domains. In these domains, pretreatment quality of life scores were significantly higher in the radiation therapy group, implying a poorer quality of life status at the initiation of treatment. In post hoc analysis, the global health

domain was significantly more improved ($P = 0.03$) by chemoradiation. Peripheral neuropathy was not increased by chemoradiation.

Implications: Chemoradiation therapy improved quality of life more than radiation therapy in certain domains. This allows for selection of chemoradiation as a treatment option in situations where quality of life is the end point of treatment. (*Clin Ther.* 2015;37:2324–2331) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: Cervical cancer, Chemoradiation, Quality of life.

INTRODUCTION

Cervical cancer remains common in developing countries, where the majority of cases occur.¹ In these developing countries, a high incidence of advanced-stage cervical cancer is found. The advanced stage is not amenable to surgery, and radiation therapy has been the treatment of choice.² In 1995, on the basis of 5 randomized controlled trials, the National Cancer Institute recommended that chemoradiation therapy be the preferred treatment for advanced-stage cervical cancer.³ A meta-analysis by Green et al⁴ of available studies showed a 5-year survival benefit of 29% in all stages of cervical cancer for chemoradiation therapy compared with radiation therapy. In a separate meta-analysis, Lukka et al⁵ calculated a 26% survival benefit, but subsequent limitations—for example, omission of unpublished studies—challenged this finding.^{5,6} A Cochrane review calculated a survival benefit of 13% across all stages of cervical cancer treated with chemoradiation therapy.⁷ Limitations in

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all of these meta-analyses were differences in study designs, accrual rates, and treatment schedules. Additional limitations included heterogeneity of the control arms of the studies, including the use of previously conducted studies as controls. These limitations were addressed by performing an individual patient data analysis. This individual patient data analysis found there was a 9% survival benefit with chemoradiation therapy in all stages of cervical cancer. The effect of chemoradiation therapy on survival decreased with increasing tumor stage, with estimated absolute survival benefits of 10% (stage IA–IIA), 7% (stage IIB), and 3% (stage III–IVA) at 5 years.⁸

Despite increased toxicity, chemoradiation therapy is still widely accepted.⁹ The increased toxicity relates to specifically increased grade 3 and 4 hematologic toxicity (2-fold increases) and gastrointestinal (3-fold increases) events in the chemoradiation therapy group.¹⁰ The presence of physician-recorded toxicity correlates poorly with patient-reported quality of life.¹¹ A meta-analysis of chemoradiation therapy toxicity suggests that although the acute toxicity was acceptable, additional studies on the toxicity-related impact on quality of life are needed.¹⁰ The present study aims to describe the impact on quality of life of radiation therapy or chemoradiation therapy for women with cervical cancer treated at Tygerberg Hospital, South Africa.

METHODS

Inclusion Criteria

Newly diagnosed cervical cancer patients referred to the Unit of Gynaecologic Oncology, Tygerberg Hospital were approached to participate in the study. The unit is 1 of the 2 tertiary referral units for public-sector patients of the Western Cape Province. The Western Cape Province has a population of 5.8 million. The majority of the population (85%) does not have private insurance and are dependent on the public facilities provided by the 2 tertiary hospitals (Tygerberg Hospital and Grootte Schuur Hospital) for treatment of invasive cervical cancer.¹²

Patients were eligible if they had histologically proven cervical cancer. Women unable to provide informed consent because of psychiatric disorders were excluded. After informed consent was obtained, the patients completed the questionnaire in the language of their choice, for example, Xhosa, English, or Afrikaans.¹³ A research assistant helped patients who

could not read or write. To exclude bias, the research assistant had no medical background and was not involved in the clinical management of the patients. Patients completed the questionnaires before treatment, after completion of initial treatment, and at 3-month post-treatment follow-up. Clinical data were extracted from patient records. Ethical approval was obtained from the local committee (S12/06/174).

Confounding variables that could affect quality of life were included in statistical analysis. These were age, race, educational level, employment status, income, stage of cervical cancer, and HIV status. Employment status, marital status, race, income, and educational levels were self-reported by patients. A poverty line income of ZAR3500 per month was used.¹²

The treatment protocol at Tygerberg Hospital for patients with advanced stage IB2 to IVA cervical cancer is 46 to 50 Gy in 23 to 25 fractions of external beam radiation therapy (EBRT). This is delivered to the pelvis with concurrent weekly cisplatin (40 mg/m²) for 4 to 6 cycles and high-dose radiation brachytherapy at 20 to 26 Gy in 4 to 5 fractions starting in week 5 of EBRT. The cervix, uterus, parametria, and pelvic lymph nodes up to and including the common iliac are delineated by a planning computed tomography scan. The para-aortic lymph nodes (PAN) were delineated up to the renal hilum if the common iliac or lower PANs are involved on imaging. This volume is conformally mapped on the XiO Radiation Treatment Planning System (Computerized Medical Systems, Inc, Maryland Heights, Missouri).

The treatment protocol was EBRT at 2 Gy fractions 5 days a week or, alternatively, at 1.8 Gy fractions if the patient has a history of abdominal surgery, is HIV-positive, or has a PAN field. The PAN field receives 45 Gy and the pelvic area receives 50.4 Gy. Patients who have poor performance status or very advanced local disease with bilateral hydronephrosis or renal compromise are prescribed 40 Gy in 15 fractions at 2.67 Gy fractions. Treatment is with an 18-mV linear accelerator with multiple shielding capabilities. During or after the fifth week of EBRT, each patient is examined under anesthesia. A Smit sleeve is placed in the cervical os, and high-dose rate brachytherapy is planned to a total dose of 20 to 26 Gy in 4 to 5 fractions. The dose is delivered by a Varian GammaMed machine (Varian Medical Systems, Palo Alto, California). Chemotherapy is prescribed based on an evaluation of renal function

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before treatment. If the creatinine clearance and glomerular filtration rate is 60 mL/min, then weekly cisplatin (40 mg/m²) for a minimum of 4 cycles is prescribed. If it is 50 to 60 mL/min, then the dose is reduced by 25% per cycle, and if the rate is <50 mL/min, then cisplatin is omitted. If the glomerular filtration rate is 30 to 50 mL/min, then carboplatin is given weekly by calculating a dose based on area under the curve of 2 as an alternative.

Chemotherapy is delayed if the neutrophil count falls below 1000/L, if the platelet count falls below 75,000/L, or if the patient develops grade 3 gastrointestinal tract toxicity. Chemotherapy is discontinued if the glomerular filtration rate falls below 50 mL/min or decreases by >50%, if the neutrophil or platelet count does not recover, or if the patient develops persistent grade 3 gastrointestinal tract toxicity. Patients on hypofractionated radiation schedules and patients who have serious medical comorbidities (eg, active tuberculosis) do not receive chemotherapy.

At the time of diagnosis, patients who have never or who have recently been tested for HIV are referred for counseling and testing. HIV-positive patients begin prophylaxis with cotrimoxazole, and those not already on treatment commence antiretroviral therapy. HIV-positive patients receive the same treatment for cervical cancer as HIV-negative patients, but the dose per fraction is reduced to 1.8 Gy and, if the CD4 count is <200 cells/L, chemotherapy is omitted. Patients whose CD4 count is <150 cells/L might not tolerate a long course of radiation and are therefore treated on a shortened regimen dependent on performance status.¹⁴

Questionnaires

The European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) and the Cervix Cancer Module (QLQ-CX24) were used. The EORTC QLQ-C30 consists of 30 questions grouped into 5 functional scales (ie, physical, role, emotional, social, and cognitive), 3 symptom scales (ie, fatigue, nausea and vomiting, and pain), an overall quality of life scale, and 6 individual items (ie, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The EORTC QLQ-C30 was analyzed according to the procedures recommended by the EORTC Quality of Life group. Higher scores on the QLQ-C30 functioning scales and the overall quality of

life scale indicate a higher level of functioning and a better quality of life. Higher scores on the symptom scales or individual item scales represent a higher level of symptoms or problem.¹⁵ The EORTC QLQ-CX24 module includes 3 multi-item scales (symptom experience, body image, and sexual function) and 5 single-item scales (lymphedema, lower back pain, menopausal symptoms, tingling and numbness, and sexual enjoyment). Higher scores are equivalent to worse or more symptoms, except items 49 and 54 for which higher score indicates better quality of life.¹⁶

Statistical Analysis

Descriptive statistics was used to characterize confounding sociodemographic and medical variables. Data are presented as medians and were analyzed using the nonparametric Kruskal-Wallis test to detect change in the different domains during the study period. In case of statistical difference, post hoc analysis was done with Fisher's Least Significant Difference test. χ^2 Tests were used for categorical data. A *P* value < 0.05 was considered to be significant. Statistical analysis was performed using STATISTICA software, version 12 (StatSoft, Inc, Tulsa, Oklahoma).

RESULTS

Demographic Data

A total of 219 women completed pretreatment questionnaires, 134 post treatment, and 96 at 3-month follow-up visit. The total study group had an incidence of 22% positive HIV status. There was a significant difference in loss to follow-up between HIV-positive and HIV-negative patients (Figure 1). The women undergoing radiation therapy or chemoradiation therapy were further analyzed. Mean ages of the 2 treatment groups were similar. The radiation therapy group had significantly more pensioners (women older than 65 years of age). Mean monthly incomes were similar, but significantly more women in the radiation therapy had incomes below the poverty line. HIV-positive women were treated twice as often with radiation therapy than HIV-negative women (Table 1). Stage distribution was significantly different between the radiation therapy and chemoradiation therapy groups (Figure 2). The distribution shows more stage IIB women received chemoradiation therapy than radiation therapy. This ratio is reversed in the case of stage IIIB women.

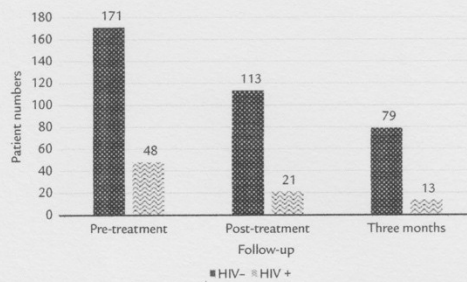


Figure 1. Follow-up of HIV-negative vs HIV-positive women during the study period.

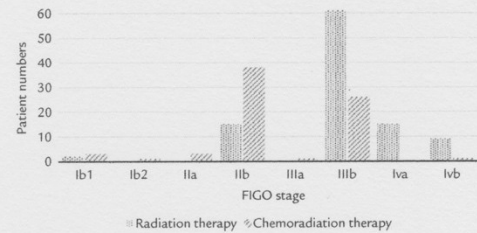


Figure 2. International Federation of Gynecology and Obstetrics (FIGO) stage distribution of groups.

Table I. Demographic characteristics of women treated with radiation therapy and chemoradiation therapy.

Characteristics	RT (n = 102)	CR (n = 73)	P Value
Age, y	51.72	47.66	NS
Mean education level, grade	7	8	<0.01
Race, %			<0.01
Mixed ethnicity	53	47	
Black	71	29	
White	22	78	
Income, ZAR	1178.81	1749.34	NS
HIV+, %	25	12	<0.05
Below poverty line of ZAR3500, %	61	35	<0.05
Marital state, %			NS
Single	65	35	
Married	45.5	54.5	
Widow	74	26	
Divorced	57	43	
Employment, %			<0.01
Employed	45	55	
Retired	83	17	
Unemployed	56	44	

CR = chemoradiation therapy; RT = radiation therapy

Radiation therapy was used significantly more in women with stage IV disease.

Comparison of Quality of Life Changes Between Treatment Groups

There was significantly more change in physical functioning and global health in the chemoradiation therapy group over time. Improvements in the quality of life domains of pain, fatigue, appetite loss, nausea and vomiting, and social function were significantly better in the chemoradiation therapy group. In all of these domains, the pretreatment scores of radiation therapy were statistically higher than the chemoradiation therapy group. This implies a worse quality of life in symptom domains and better social function in the radiation therapy group (Table II). In the majority of domains, there was no significant difference in the change in quality of life during the study period. The change in quality of life domains that were significantly different between the 2 treatment groups included physical function, pain, fatigue, appetite loss, nausea and vomiting, and global health (Figures 3–8). Peripheral neuropathy remained unchanged during the study period (Figure 9).

DISCUSSION

The study on women treated for cervical cancer at Tygerberg Hospital found demographic differences between women treated with radiation therapy and chemoradiation therapy. Monthly incomes were similar, but there were more women with incomes below the poverty line in the radiation therapy group. Black

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Table II. Comparison of change in quality of life during the study period between radiation therapy and chemoradiation therapy groups. Data are *P* values.

Quality of Life Domain	RT (n = 102)	CR (n = 73)	RT vs CR
Physical function	<0.01	<0.01	<0.01
Role function	<0.01	<0.01	NS
Cognitive function	<0.01	<0.01	NS
Emotional role	<0.01	<0.01	NS
Social role	<0.05	<0.01	NS
Dyspnea	<0.01	NS	NS
Pain	<0.01	<0.01	<0.05
Fatigue	<0.01	<0.01	<0.05
Insomnia	<0.01	<0.01	NS
Appetite loss	NS	<0.05	<0.01
Nausea and vomiting	<0.01	NS	<0.05
Constipation	<0.01	<0.01	NS
Diarrhea	NS	NS	NS
Financial difficulties	NS	NS	NS
Global health status	<0.01	<0.01	<0.05
Symptom experience	<0.01	<0.01	NS
Lymphedema	NS	NS	NS
Peripheral neuropathy	NS	NS	NS
Menopausal symptoms	NS	NS	NS
Body image	<0.01	<0.01	NS
Sexual worry	NS	<0.01	NS
Sexual activity	<0.05	<0.05	NS
Sexual or vaginal functioning	NS	NS	NS
Sexual enjoyment	NS	NS	NS

CR = chemoradiation therapy; RT = radiation therapy.

pensioners underwent radiation therapy more than chemoradiation therapy. The stage distribution was significantly different among the treatment groups, and radiation therapy was used more in stage IIIB and IV disease. HIV-positive women received radiation therapy significantly more than HIV-negative women. The change in the majority of quality of life domains during the study period was not significantly different between

the treatment groups. Despite the abject poverty in both groups demonstrated by low income, financial-related quality of life did not change during the study.

Chemoradiation therapy was associated with statistically more improvement in the domains of physical function, pain, fatigue, appetite loss, social role, global health status, and nausea and vomiting. Women in the radiation therapy group had higher pretreatment scores in these domains than their chemoradiation therapy counterparts. These differences in the pretreatment domains are the result of clinical treatment decisions. Although the pretreatment quality of life scores were unknown to the presiding clinicians, women with a better initial quality of life were selected to receive chemoradiation therapy. This is related to increased toxicity of chemoradiation therapy and the presiding clinician electing not to expose women who were already in a medically compromised pretreatment situation to be exposed to additional compromising chemoradiation therapy.

The fact that HIV-positive patients received radiation therapy twice as often as chemoradiation therapy illustrates the effect of clinicians selecting patients in better general health to receive chemoradiation therapy. In a previous study, HIV-positive women with cervical cancer tolerated the chemotherapy component of chemoradiation therapy poorly and failed to complete the treatment.⁸ In the present study, women with advanced stage (IIIB and IV) received radiation therapy significantly

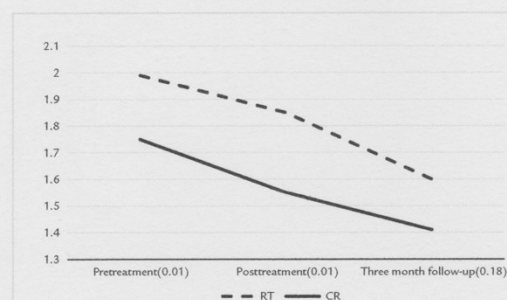


Figure 3. Physical function domain during the study period. CT = chemoradiation therapy; RT = radiation therapy. Value in brackets after each treatment time is the *P* value of the comparative scores between the 2 treatment groups.

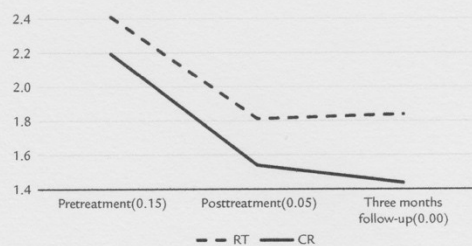


Figure 4. Pain domain during the study period. CT = chemoradiation therapy; RT = radiation therapy. Value in brackets after each treatment time is the *P* value of the comparative scores between the 2 treatment groups.

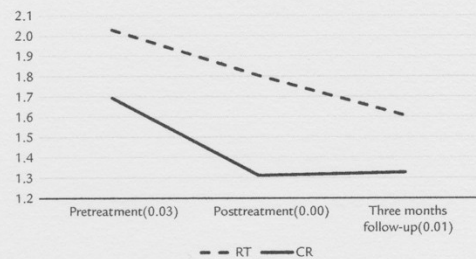


Figure 6. Appetite loss during the study period. CT = chemoradiation therapy; RT = radiation therapy. Value in brackets after each treatment time is the *P* value of the comparative scores between the 2 treatment groups.

more often than chemoradiation therapy. This selection bias could be related to treatment in the advanced stages aimed at palliation and not possible cure. In a palliative situation, addition toxicity is not warranted. Despite the reported increase in toxicity with chemoradiation therapy, the treatment improved the quality of life more than radiation therapy in certain domains, such as appetite loss and pain. Paradoxically, exposure to chemoradiation therapy did not increase chemotherapy-related fatigue, appetite loss, or nausea and vomiting. Peripheral neuropathy was not significantly changed by either treatment. The use of cisplatin in a dose not exceeding 250 to 350 mg/m² might explain the absence of peripheral neuropathy. Peripheral neuropathy

is experienced if the cumulative dose of cisplatin exceeds 250 to 350 mg/m².¹⁷

Despite documented survival benefit, the use of chemoradiation therapy requires a close analysis of available data. The initial recommendation of the National Cancer Institute for chemoradiation therapy as the preferred treatment of locally advanced cervical cancer was based on studies of patients with no para-aortic lymph node metastases. All randomized controlled trials cited by the National Cancer Institute had para-aortic lymph node metastasis as exclusion criteria.³ Para-aortic lymph node metastases occur in 16% to 38% of stage III

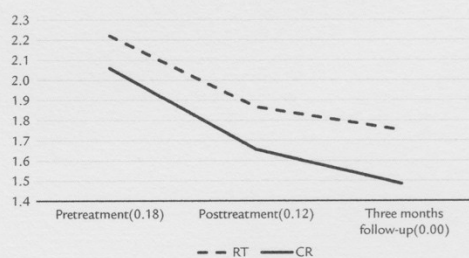


Figure 5. Fatigue domain during the study period. CT = chemoradiation therapy; RT = radiation therapy. Value in brackets after each treatment time is the *P* value of the comparative scores between the 2 treatment groups.

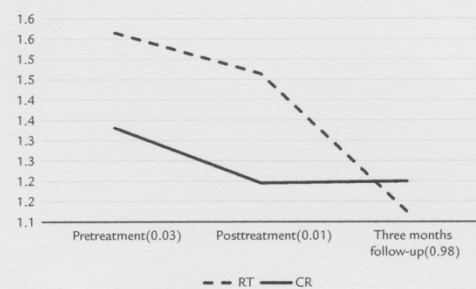


Figure 7. Nausea and vomiting during the study period. CT = chemoradiation therapy; RT = radiation therapy. Value in brackets after each treatment time is the *P* value of the comparative scores between the 2 treatment groups.

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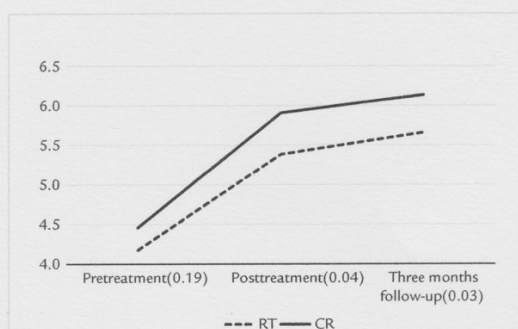


Figure 8. Global health scores during the study period. CT = chemoradiation therapy; RT = radiation therapy. Value in brackets after each treatment time is the *P* value of the comparative scores between the 2 treatment groups.

and IV cervical cancers.¹⁸ The majority of advanced cervical cancer cases occur in resource-constrained developing countries. Curative chemoradiation therapy as treatment would require routine imaging of the para-aortic area to identify patients requiring para-aortic radiation; resource constraints on imaging facilities pose a problem.¹⁹ The Cochrane review of individual patient analysis calculated survival and disease-free survival of chemoradiation therapy in stage III and IVA cervical cancers are not statistically significant.⁸

Limitations of the present study are small numbers that preclude quality of life analysis of subgroups.

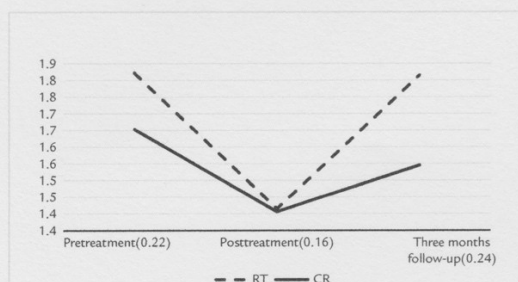


Figure 9. Peripheral neuropathy during the study period. CT = chemoradiation therapy; RT = radiation therapy. Value in brackets after each treatment time is the *P* value of the comparative scores between the 2 treatment groups.

Subanalysis in stage III and IV disease could provide clarity of possible differences in quality of life changes between radiation therapy and chemoradiation therapy. The short follow-up of 3 months post-treatment limits conclusions on the long-term quality of life. Because radiation toxicity can occur after protracted time periods since treatment, additional studies are needed. Because quality of life was a secondary outcome in a study where treatment was nonrandomized, treatment selection bias led to patients with initial poorer quality of life being selected to undergo radiation therapy. As the survival benefit of chemoradiation therapy is well documented, additional randomized controlled trials to compare radiation therapy and chemoradiation therapy with quality of life as a primary end point are unlikely.

CONCLUSIONS

Chemoradiation therapy is an appropriate treatment in selected patients. The enhancement of quality of life of women with cervical cancer treated with radiation therapy and chemoradiation therapy is of a similar magnitude in the majority of quality of life domains. In selected domains, chemoradiation therapy is associated with better improvement in quality of life than radiation therapy. Selection bias exists in the initial selection of patients to receive either therapy. This bias is related to the presiding clinician selecting radiation therapy in patients with poorer general health and advanced-stage disease. HIV-positive patients, because of treatment-related complications, are more likely to receive radiation therapy than chemoradiation therapy. Despite reported increased toxicity in women treated with chemoradiation therapy, these toxicities did not adversely affect quality of life.

In the present study, advanced-stage disease was more often treated with radiation therapy. Given the favorable outcomes on quality of life with use of chemoradiation therapy, additional study is required to extend chemoradiation therapy in advanced stages where palliation is the aim of treatment. The enhancement of quality of life in these women should be weighed against possible toxicity. The limited increased nonsignificant survival benefit of 3% in 5-year survival when using chemoradiation therapy in stage III and IV disease requires careful consideration in developing countries with a high incidence of advanced-stage cervical cancer, concurrent AIDS, and constraints on resources.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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Address correspondence to: George du Toit, MBChB, MMed, FCOG/LKOG(SA), Unit of Gynaecological Oncology, Tygerberg Hospital, University of Stellenbosch, 50 van der Stelstraat, Stellenbosch, Western Cape Province 7600, South Africa. E-mail: dutoitg@worldonline.co.za

Chapter 5. A prospective study of human immunodeficiency virus-positive women with cervical cancer treated at Tygerberg Hospital

Introduction

Invasive cervical cancer is an AIDS-defining disease-positive women with cervical cancer poses specific challenges in treatment with regard to toxicity associated with radiation and chemo radiation therapy. HIV-positive women with cervical cancer tolerate the addition of chemotherapy to radiation therapy poorly. This results in incomplete treatment due to toxicity and no survival benefit^(1,2). The impact on quality of life of the addition of chemotherapy in these circumstances is requires evaluation. The research is presented as two articles. The initial article, a cross sectional study, describe the demographical data and QOL HIV-positive women with newly diagnosed cervical cancer. The second article, a prospective study, describes the QOL outcome of HIV-positive women treated for cervical cancer^(3,4).

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Contextual quality of life of HIV-positive patients with cervical carcinoma at Tygerberg Hospital

Du Toit GC, MBChB, MMed, FCOG/LKOG(SA), Part-Time Consultant Lecturer

Unit of Gynaecological Oncology, Tygerberg Hospital; University of Stellenbosch, Stellenbosch

Kidd M, PhD, Statistical Consultant and Professor

Centre for Statistical Consultation; University of Stellenbosch, Stellenbosch

Correspondence to: George du Toit, e-mail: dutoitg@worldonline.co.za

Keywords: human immunodeficiency virus, cervical carcinoma, quality of life, advanced stage

Abstract

Objective: In South Africa, the majority of cervical carcinoma cases present when they are in the advanced stage. Concomitant HIV/AIDS further compromise patient health. Data on the impact of HIV/AIDS on the quality of life of cases with advanced cervical carcinoma are lacking. Contextual factors, e.g. patient's educational level and income, influence their experience of quality of life.

Design: A cross-sectional study was carried out on the quality of life of newly diagnosed cases of cervical carcinoma. Self-administered questionnaires were completed by patients and other contextual factors (e.g. age, educational level, socio-economic status and clinical information), were obtained from patient folders.

Setting and subjects: Newly diagnosed cases of invasive cervical carcinoma who presented at the Gynaecological Oncology Unit, Tygerberg Hospital, were included in the study. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (QLQ)-C30 version 3 and QLQ-CX24 were used.

Results: The total study cohort of 73 patients (HIV-negative and HIV-positive) had a median age of 49 (28.3- 85.2 years). Of the patients, 7.1% had no formal education. The cohort had an unemployment rate of 41.5%, and 14.2% were pensioners. The marital state was predominantly single persons (31.4%), with a mean monthly income of R 1 373 (R0-14 000). Advanced stage of the disease was present in more than 50% of cases, and 32.2% were stage IIIB. Sixteen patients were HIV positive with an HIV-positive incidence of 22%. The comparative quality-of-life domains of HIV-negative and HIV-positive cases were statistically equal. Advanced stage, as a contextual factor, impacted significantly on a number of quality-of-life domains. These domains are amenable to medication.

Conclusion: HIV/AIDS did not adversely influence the quality of life of the newly diagnosed cervical carcinoma cases. In this regard, stage of disease had a significant impact on the domains of pain, insomnia, nausea and vomiting, appetite loss and constipation. These aspects are amenable to treatment. Cognitive function was adversely influenced by increasing age, poor education and a low monthly income. When giving support to patients with regard to enhancing their quality of life, this should be recognised and communicated to them.

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Introduction

The majority of advanced-stage cervical carcinoma cases occur in developing countries. In these countries, advanced stage at presentation is associated with high mortality rates. The world age-standardised incidence rate (ASIR) for cervical carcinoma is 15.2/100 000, and the age-standardised mortality rate (ASMR) is 7.8/100 000. The predominance of early-stage disease in developed countries, e.g. the USA, is reflected by an ASMR of 1.7/100 000. Southern Africa has an ASIR of 26.8/100 000, with an ASMR of 14.8/100 000. South African studies report a high

incidence of advanced disease and poor five-year survival.¹ Cronje reported a 65%, and Moodley an 80%, incidence of advanced disease.^{2,3} A 35% five-year survival in stage III disease was documented.⁴

Background

The quality of life of women with advanced cervical carcinoma is influenced by the disease and its subsequent treatment. In this situation, limited survival, despite treatment, warrants an assessment of treatment-related impact on quality of life. Concomitant human immunodeficiency virus (HIV)

infection further compromises health and impacts on treatment, with a possible influence on quality of life. Invasive cervical carcinoma and acquired immune deficiency syndrome (AIDS) are associated diseases. The Centers for Disease Control and Prevention identifies invasive cervical carcinoma as an AIDS-defining condition. Invasive cervical carcinoma is designated as AIDS stage IV disease in the World Health Organization clinical staging of HIV/AIDS.^{5,6} Chemoradiation is the current treatment for advanced cervical carcinoma.

HIV-positive women with cervical carcinoma have a poor prognosis when compared to their HIV-negative counterparts. This is because of the advanced stage of the disease on presentation and a lesser chance of completing treatment. Chemoradiation confers a limited survival benefit of 3%, compared to radiation alone in stage IIIB cervical carcinoma. A lower CD4 count is associated with failure to complete chemotherapy in HIV-positive women. Simonds suggests omitting chemotherapy as a reasonable option to enable the completion of radiotherapy.⁷ The identification of treatment-related changes of quality of life should further influence future treatment decisions. To assess these changes, it is necessary to determine quality of life prior to treatment.

HIV status is a confounding, contextual factor in the quality of life of women with cervical carcinoma. Ashing-Giwa introduced the concept of contextual quality of life as a comprehensive framework, developed to expand the traditional quality-of-life framework.⁸ This means that the cultural and socio-economic status of patients should be taken into account when assessing their quality of life. The inclusion of these contextual domains may increase the validity and utility of the quality-of-life framework to assess overall functioning in ethnically and socio-economically diverse patients with cancer. Contextual factors in this framework include socio-ecological factors, cultural background, demographic details and the healthcare system within which the patient is managed.⁸ Contextual quality-of-life factors, identified in patients with breast carcinoma, could be improved with interventions such as community-based support groups.⁹ Contextual factors that are relevant to a quality-of-life study in a developing country include age, education, monthly income and stage of cervical carcinoma.¹⁰

In a Thai study, the quality of life of women with newly diagnosed cervical carcinoma was lower than that of the general healthy population. This study identified lower socio-economic status and lower educational levels in women with cervical carcinoma. The mean age of these women was 52.4 years and 37% presented with stage III and IV disease.¹¹ In contrast to these results, Pasek et al reported that Polish women with newly diagnosed cervical carcinoma had a better educational level and socio-economic status. In the

Polish study, stage III and IV disease occurred in 53% of cases.¹² In comparison to these studies, the mean age of South African women diagnosed with stage III and IV cancer (58-94%) was 50-53 years.^{2,3}

Current studies on the quality of life in women with newly diagnosed cervical carcinoma in South Africa are lacking. Studies on the contextual quality of life of HIV-positive and HIV-negative women with cervical carcinoma in a developing country, such as South Africa, are limited. The main objective of the study was to compare the quality of life of these women at the time of diagnosis. A second aim was to determine the influence of contextual factors on quality of life in this cohort of women with newly diagnosed cervical carcinoma.

Method

This was a cross-sectional study that compared the quality of life of HIV-positive and HIV-negative cervical carcinoma cases at diagnosis. The study also describes the influence of the contextual factors on the quality of life of these patients. All women with newly diagnosed cervical carcinoma, presenting at the Unit of Gynaecological Oncology of Tygerberg Hospital from October 2012 to March 2013, were approached for enrolment in the study. The patients received written information, in the language of their choice, on the method and goal of the study. This included the nature of the questionnaire content. Subsequent informed consent was obtained.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ)-C30 version 3 and QLQ-CX24 were used. The 30-item QLQ-C30 is a psychometrically validated, cross-culturally accepted questionnaire, and is applicable to a broad spectrum of patients with cancer as a core questionnaire. This instrument consists of five function scales (physical, role, emotional, cognitive and social); three symptom scales (fatigue, nausea or emesis and pain); six single-item scales (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea and financial impact), and a global quality-of-life scale. The QLQ-CX24 is a cervical carcinoma-specific questionnaire. Its 24 items are summarised in three scales, namely symptom experience, body image, and sexual and vaginal functioning. The other dimensions of this questionnaire are single-item scales of lymphoedema, peripheral neuropathy, menopausal symptoms, sexual worry, sexual activity and sexual enjoyment.¹³

During the study, the questionnaires were self-administered by patients in their language of choice (English, isiXhosa and Afrikaans). Illiterate patients were assisted during completion of the questionnaires. Demographic, clinical and socio-economic data were

Original Research: Contextual quality of life of HIV-positive patients

obtained from patient folders. Ethics approval was acquired from the Health Research Ethics Committee of Stellenbosch University (No S12/06/174). Means and standard deviations were employed to describe the study groups in the case of continuous data. Frequencies and percentages were used for categorical data. Statistical analyses were carried out using the chi-square test or Fischer's exact test for categorical data, and Student's t-test for continuous data. Pearson's correlation coefficient and Spearman's rank correlation coefficient were used to correlate domains of quality of life with contextual factors. A p value of ≤ 0.05 was regarded as statistically significant.

Results

The total study cohort of 73 patients (HIV negative and HIV positive) had a median age of 49 (28.3-85.2) years. 7.1% of the patients had no formal education (Figure 1). The cohort had an unemployment rate of 41.56%. 14.2% were pensioners. The marital state was predominantly single persons (31.43%), with a mean monthly income of R1 373 (R0-14 000). Advanced stage of disease was present in more than 50% of cases, and

32.2% were stage IIIb (Figure 2). A total of 16 patients were HIV positive, with an HIV incidence of 22%. The demographic features of the HIV-negative and HIV-positive groups were statistically similar (Table I).

The comparative quality-of-life domains of HIV-positive and HIV-negative cases were statistically equal (Table II). The contextual influence of age, educational level, monthly income and stage on the quality of life of the total study group is depicted in Table III. Advanced stage of cancer had a statistically significantly negative impact on the domains of pain, fatigue, insomnia, nausea and vomiting, appetite loss and constipation. Cognitive function was adversely influenced by increasing age, poor education and low monthly income.

Discussion

In the current study, HIV-positive and HIV-negative women with newly diagnosed cervical carcinoma had a similar quality of life. Advanced stage of carcinoma and low levels of education influenced the quality of life of the total study cohort. The quality-of-life domains that were influenced by advanced-stage cancer included pain, fatigue, insomnia, appetite loss, nausea, vomiting, constipation, body image, sexual activity and sexual enjoyment. Educational levels influenced the domains of physical symptoms, cognitive function and menopausal symptoms.

Demographic data from previous studies on cervical carcinoma in South Africa have consistently documented the younger age of HIV-positive cervical cases (Table IV). A consistent mean age of 41-44 years of HIV-positive cases was reported in these studies. In the current study, the nine-year age difference between the HIV-negative and HIV-positive subjects was similar to that reported in these studies. In

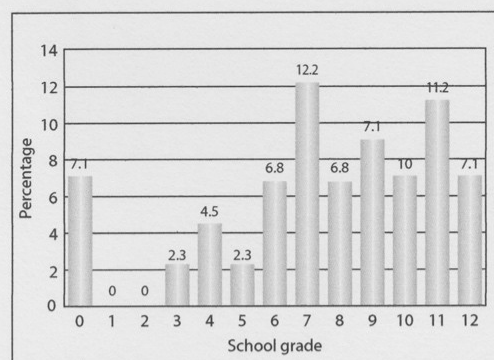


Figure 1: Education level of the study group

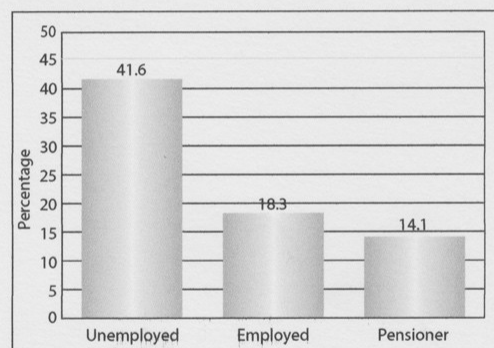


Figure 2: Employment status of the study group

Table I: Demographic data of HIV-negative and HIV-positive patients with newly diagnosed cervical carcinoma

Demographic data	HIV-negative (n = 57)	HIV-positive (n = 16)	p-value
Age (years)	51.23	44.44	0.06
Monthly income (Rands)	1 733.06	1 272.06	0.46
Stage of disease			0.55
Education (grade passed)	7	8	0.16
Marital status			0.03
Race			0.00042*
Employment			0.15

HIV: human-immunodeficiency virus

* Coloured patients (50% were HIV-positive) and black patients (80% were HIV-positive)

Quality of life of HIV-positive patients

Table II: Comparative quality-of-life domains

Quality-of-life domains	HIV-negative and HIV-positive patients with newly diagnosed cervical carcinoma		
	HIV-negative	HIV-positive	p-value
Physical functioning	9.68± 3.66	10.87 ± 3.59	0.25
Role functioning	3.89± 1.82	4.06 ± 2.14	0.75
Emotional functioning	8.31 ± 3.75	9.68± 3.68	0.18
Cognitive functioning	3.73 ± 1.57	4.20± 1.97	0.34
Social functioning	3.50 ± 1.59	4.00 ± 1.75	0.28
Global health and quality of life	9.40 ± 6.85	6.18±2.97	0.07
Fatigue	6.73 ± 2.49	7.81 ± 2.92	0.14
Nausea and emesis	2.73± 1.38	3.33 ± 1.49	0.15
Pain	4.66± 2.29	4.87 ± 2.33	0.75
Dyspnoea	1.70± 1.05	1.62 ± 1.20	0.80
Insomnia	2.05± 1.25	2.31 ± 1.30	0.47
Appetite loss	1.64± 1.00	1.81 ± 1.10	0.58
Constipation	2.42 ± 1.26	2.43 ± 1.36	0.97
Diarrhoea	1.17 ± 0.46	1.43 ± 0.96	0.13
Financial difficulties	1.73 ± 1.02	2.06 ± 1.06	0.27
Symptom experience	20.64± 5.95	23.00 ± 5.54	0.16
Body image	5.26 ± 2.49	6.68 ± 2.79	0.05
Sexual and vaginal function	8.38 ± 0.91	8.33 ± 1.34	0.93
Lymphoedema	1.52 ± 0.88	1.81 ± 1.22	0.30
Peripheral neuropathy	1.59±0.12	2.38 ± 0.23	0.0042
Menopausal symptoms	1.92 ± 0.13	2.43± 0.25	0.09
Sexual worry	2.04 ± 0.17	2.06±0.32	0.94
Sexual activity	1.36 ± 0.09	1.31 ± 0.18	0.78
Sexual enjoyment	2.46 ± 1.05	2.00± 1.09	0.39

the aforementioned studies, Simonds recorded statistically significant. higher-percentage, advanced-stage presentation in HIV-positive cases. The Moodley and Lomalisa studies showed no difference in stage distribution.^{3,7,1} The current study's findings on stage concur with the latter two studies. In the current study, a high incidence of stage IIb cases occurred (32%). In previous South African studies, Cronje reported a 59%, and Moodley a 93%, incidence of advanced-stage cancer upon presentation.^{1,1}

In the current study, HIV/AIDS infection did not impair the quality of life of patients with Invasive cervical carcinoma. The impact of HIV/AIDS on other malignancies, e.g. lymphoma, revealed that HIV-positive patients had a worse overall quality of life and survival than that of uninfected patients. Quality-of-life differences were more marked in the areas of functional, physical and social well-being than in the area of emotional well-being. HIV-positive lymphoma patients had a lower income than uninfected patients.

HIV-positive lymphoma patients had a worse quality of life and survival than uninfected patients, because of a combination of co-morbidity, aggressive histology and lack of social support. However, their emotional well-being was comparable to that of uninfected lymphoma patients, and better than the historical norms for HIV-positive subjects.¹

Developing regions of the world, such as South-East Asia, Central America and the Caribbean, have incidence rates of cervical carcinoma which are similar to those in South Africa.¹ Demographic data from Thailand show that people with cervical carcinoma had a poor education. Twenty-one per cent had no education and 58% cases had attained an education level lower than that of high school.¹ The current study documented a high unemployment rate of 41.6%, and an uneducated rate of 7.1%. This, together with the study findings from Thailand, confirms advanced-stage cervical carcinoma as a disease that occurs predominantly in lower socioeconomic population groups with poor educational

Table III: Correlation between the contextual factors and quality-of-life domains

Quality-of-life domains	Age	Education	Monthly income	Stage
Physical	0.31*	-0.4*	-0.12	0.21
Role	-0.02	-0.08	-0.17	-0.01
Dyspnoea	0.22	-0.24*	-0.05	-0.08
Pain	0.04	-0.29	-0.17	0.34*
Fatigue	0.13	-0.26	-0.11	0.29*
Insomnia	0.07	-0.12	-0.15	0.27*
Appetite loss	-0.07	-0.2	-0.11	0.34*
Nausea and vomiting	-0.11	-0.08	-0.16	0.31*
Constipation	-0.03	-0.15	-0.21	0.28*
Diarrhoea	0.03	0.08	-0.01	0.01
Cognitive	0.27*	-0.36*	-0.24*	0.14
Emotional	-0.16	0.06	0	0.12
Social	-0.15	-0.07	-0.03	0.02
Financial difficulties	-0.25*	0.21	-0.06	-0.16
Global health status	0.23	-0.16	0.07	-0.07
Symptom experience	0.02	-0.12	-0.06	0.24*
Lymphoedema	0.28	0	-0.08	0.22
Peripheral neuropathy	0	-0.14	-0.06	-0.1
Menopausal symptoms	0.04	-0.25*	0.1	0.09
Body image	-0.09	-0.11	-0.11	0.25*
Sexual worry	-0.34*	0.08	-0.06	0
Sexual activity	-0.37*	0.21	0.06	-0.32*
Sexual enjoyment	-0.13	-0.02	-0.36	-0.14

* Statistically significant

Table IV: Previous South African studies on cervical carcinoma in patients who were human immunodeficiency virus-positive

Author	N	HIV-positive (%)	Mean age (years)		Stage III and IV (%)	
			HIV-negative	HIV-positive	HIV-negative	HIV-positive
Lomalisa ¹⁰	836	7.2	53*	44*	55	65
Moodley ¹¹	271	21.8	54*	41*	94	64
Simonds ¹²	383	18.2	50*	41*	58*	65*

HIV: human immunodeficiency virus

* Statistically significant

levels. The contextual factors of poor education level and unemployment had a direct effect on the quality of life of the patients at diagnosis in the Thai study.

The limitation of the current study was the low number (16) of HIV-positive cases. The stage of AIDS and CD4 counts could also be relevant to the quality of life experienced by the women. This was a further limitation of the current study.

Conclusion

The current study documented that the presence of HIV/AIDS in newly diagnosed cases of cervical

cancer did not influence their quality of life. The most important contextual factor that negatively influenced their quality of life was advanced-stage cancer and education level. Specific attention to alleviating the symptoms of pain, constipation, nausea and vomiting in these cases is required to improve their quality of life. A further finding was the significant impact of menopausal symptoms which had a direct correlation with the poor education level of the patients. Adequate patient information with regard to menopausal symptom treatment options is an easily attainable intervention. Cognitive function was adversely influenced by increasing age, poor education

and low monthly income. To enhance the quality of life of patients, this should be recognised when communicating with them. Future research could include tailored support to improve quality of life. This must focus on supporting patients and take cognisance of their poor socio-economic circumstances and low education level.

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A prospective study of demographic features and quality of life in HIV-positive women with cervical cancer treated at Tygerberg Hospital

Authors:

George du Toit¹
Martin Kidd²

Affiliations:

¹Department of Obstetrics and Gynaecology, Stellenbosch University, South Africa

²Centre for Statistical Consultation, Stellenbosch University, South Africa

Correspondence to:

George du Toit

Email:

dutoitg@worldonline.co.za

Postal address:

Private Bag X1, Matieland 7602, South Africa

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Background: Cervical cancer and human immunodeficiency virus (HIV) infection/acquired immune deficiency syndrome (AIDS) both have a high incidence in South Africa. Cervical cancer treatment of HIV-positive women poses challenges. Treatment-related changes in quality of life (QOL) of such women are important to future treatment protocols.

Aim: To examine demographic data of HIV-negative and HIV-positive women at diagnosis of cervical cancer and describe their changes in QOL as a result of treatment.

Methods and materials: All newly diagnosed patients with cervical cancer at Tygerberg Hospital were approached to participate in the study. The European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) and the Cervix Cancer Module (QLQ-CX24) were used. General QOL was measured with the EORTC QLQ-C30 and cervical-specific QOL with the QLQ-CX24 questionnaire. The patients completed the questionnaire at diagnosis, on completion of treatment and at 3 months' follow-up.

Results: The study included a total of 221 women of whom 22% were HIV positive; the latter were younger and of higher educational level than the rest. Mean monthly income and stage distribution was similar between the two groups. HIV-positive patients underwent radiation therapy more commonly than chemoradiation. HIV-positive women showed statistically significantly higher loss to follow-up during the study. HIV-positive women experienced no improvement in insomnia, appetite loss, nausea, vomiting, diarrhoea, social role or any of the sexual domains. In contrast, HIV-negative women experienced statistically significant improvement in all sexual domains other than sexual/vaginal functioning. The QOL improvement of HIV-negative women was statistically significantly greater than their HIV-positive counterparts in the majority of QOL domains. Global health improved in both groups, with HIV-negative women experiencing greater improvement. HIV-positive women experienced an initial decline of peripheral neuropathy (PN) symptoms post treatment with a return to pretreatment values at 3 months' follow-up. The change in PN was statistically significant between the HIV-negative and HIV-positive women.

Conclusion: Demographic differences exist between the HIV-negative and HIV-positive groups. The differential outcome in the QOL of HIV-positive and HIV-negative women treated for cervical cancer might be related to persistence of AIDS-related symptoms on completion of cervical cancer treatment.

Introduction

The quality of life (QOL) of human immunodeficiency virus (HIV)-positive women with cervical cancer is the result of both diseases and the impact of their respective treatments. Invasive cervical cancer is an acquired immune deficiency syndrome (AIDS)-defining condition (World Health Organization stage 4).¹ AIDS is endemic in sub-Saharan Africa. The South African population has a 12% – 18% incidence of HIV positivity.² South Africa has a cervical cancer incidence rate of 26.8/100 000.³ Most South African women present at an advanced stage of the disease. Cervical cancer and HIV infection are epidemiologically related owing to the sexual transmission of both conditions. Peripheral neuropathy (PN) in HIV-infected persons occurs in 50% – 60% of cases. At autopsy, PN can be shown in all HIV-positive persons despite their having no signs or symptoms during their lifetime. Antiretroviral medication (particularly didanosine, zalcitabine and stavudine) is directly neurotoxic and results in PN identical to AIDS-associated neuropathy. The disease and its treatment synergistically increase PN. Cisplatin is the drug of choice in chemoradiation (CR) treatment of cervical cancer. Cisplatin results, in a dose-dependent fashion, in sensory PN in the stocking-glove distribution.⁴ Poor tolerance of chemotherapy for cervical

cancer by HIV-positive women results in substantially less completion of CR than their HIV-negative counterparts. The use of CR in advanced stage (III to IVA) cervical cancer in HIV-positive women has been questioned owing to the limited survival benefit.⁵ A Cochrane review shows a statistically non-significant 3% benefit in 5-year survival of CR over radiation therapy (RT) in stage III to IVA.⁶ Simonds et al.⁵ suggest that the omission of chemotherapy in these HIV-positive women with cervical cancer would result in timely completion of the full dose of radiation therapy.

A limitation of the study by Simonds et al.⁵ was the 15.4% (59 out of a cohort of 383) incidence of HIV-positive women.⁵ Data on the impact of RT on QOL of HIV-positive women with cervical cancer are lacking. The aim of the present study was to examine demographic data for HIV-negative and HIV-positive women at diagnosis of cervical cancer and to describe QOL changes in these women after treatment for cervical cancer.

Methods and materials

Inclusion criteria

Patients referred to the Unit of Gynaecologic Oncology at Tygerberg Hospital who had newly diagnosed cervical cancer were approached to participate in the study. The unit is one of two tertiary referral units for public-sector patients in Western Cape Province. The province has a population of 5.8 million. Most (85%) of the population do not have private medical insurance and are dependent on public facilities provided by two tertiary hospitals (Tygerberg Hospital and Groote Schuur Hospital) for treatment of cervical cancer.⁷ Patients were eligible for the study if they had histologically proven cervical cancer. Exclusion criteria included concurrent, or previous history of, cancers and medical disorders that might affect QOL, such as diabetes. Patients unable to provide informed consent owing to psychiatric disorders were excluded. Cervical cancer was staged according to international guidelines.⁸ Clinical management included HIV testing and initiation of antiretroviral treatment. HIV-positive women did not receive chemotherapy if their CD4 count was < 200 cells/ μ L, or active tuberculosis was present.

Questionnaires

Patients completed the questionnaire in the language of their choice (isiXhosa, English or Afrikaans) after informed consent was obtained.⁹ A research assistant helped illiterate patients. To exclude bias, the research assistant had no medical background and was not involved in clinical management of the patients. Questionnaires were completed prior to treatment, after initial treatment, and after a 3-month post-treatment period. The follow-up visits coincided with clinical follow-up of patients. Patients failing to attend visits were contacted telephonically where possible. Patient records were used to extract relevant clinical data. Ethical approval was obtained from the local committee (S12/06/174). Clinical management followed protocols as previously described.⁵ The European Organisation for

Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire (EORTC QLQ-C30) and the Cervix Cancer Module (QLQ-CX24) were both used. The EORTC QLQ-C30 consists of 30 items comprising 5 functional scales (physical, role, emotional, social and cognitive), 3 symptom scales (fatigue, nausea/vomiting and pain), an overall QOL scale, and 6 individual items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The EORTC QLQ-C30 was analysed according to the procedures recommended by the EORTC QOL Group. Higher scores on the QLQ-C30 functioning scales and the overall QOL scale indicate a better QOL. Higher scores on the symptom and individual item scales represent a decrease in QOL.¹⁰ The EORTC QLQ-CX24 includes 3 multi-item scales (symptom experience, body image, and sexual functioning) and 5 single-item scales (lymphoedema, lower back pain, menopausal symptoms, tingling and numbness, and sexual enjoyment). Higher scores indicate a decrease in QOL except for items 49 and 54 (where higher scores indicate better QOL).¹¹ The questionnaires used were translated and validated for use in South Africa.⁹

Statistical analysis

Descriptive statistics were used to characterise the study sample in terms of the contextual factors of socio-demographic and medical variables. Data presented as medians were analysed using Kruskal-Wallis tests. Post hoc analyses were done with Fisher's least significant difference (LSD) test. Chi-square tests were used for categorical data. A *p* value < 0.05 was considered to be significant. Statistical analysis was performed with the use of STATISTICA version 12 software.

Results

Demographic characteristics

The study included a total of 221 women (Table 1). HIV positivity of the study group was 22%. The mean age of the HIV-positive women was statistically significantly 7 years less than that of the HIV-negative women. Age had a normal distribution without any outliers. HIV-positive women had a higher educational grade. Racial distribution shows a statistically significant difference between black (40%), mixed race (12%) and white (0%) participants' HIV-positivity rates. Mean monthly income as well as the percentage of patients under the poverty line were not statistically significantly different between the HIV-positive and -negative groups. Single women had a statistically significantly higher rate of HIV positivity than their married, widowed and divorced counterparts. The stage distribution of HIV-negative and HIV-positive cases was not statistically significantly different. HIV-positive patients underwent RT more commonly than CR.

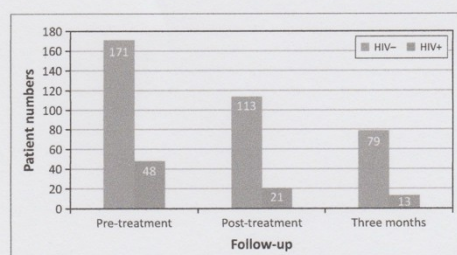
Unemployed women had a statistically significantly higher HIV-positivity rate (26%) than the employed women (23%). The loss to follow-up of HIV-positive women v. HIV-negative women during the post-treatment (56% v. 34%) and 3-month

TABLE 1: Comparative demographic data of HIV-negative and HIV-positive women (poverty line as defined by the Western Cape Provincial Government).

Characteristics	HIV-negative <i>n</i> = 173	HIV-positive <i>n</i> = 48	<i>p</i> value
Age (years)	51.34	43.94	<i>p</i> < 0.01
Mean education level (grade)	7	8	<i>p</i> < 0.05
Race (%)	-	-	<i>p</i> < 0.05
Mixed race people	88	12	-
Black people	60	40	-
White people	100	0	-
Income (ZAR)	1450	1576	NS
Below poverty line of R3500 (%)	79	21	NS
Marital state (%)	-	-	<i>p</i> < 0.05
Single	68	32	-
Married	88	12	-
Widow	86	14	-
Divorced	94	6	-
Stage distribution	-	-	NS
Treatment (%)	-	-	<i>p</i> < 0.05
Radiotherapy	75	25	-
Chemoradiation therapy	88	12	-
Employment (%)	-	-	<i>p</i> < 0.05
Employed	77	23	-
Pensioner	93	7	-
Unemployed	74	26	-

Source: Western Cape Provincial Treasury, Regional development profile City of Cape Town, 2012 [cited 2014 Jul 23]. Available from: http://www.westerncape.gov.za/assets/departments/treasury/dc0_city_of_cape_town_sep-lg_profile_02_2013.pdf

NS, not significant.

**FIGURE 1:** Follow-up of HIV-negative versus HIV-positive women over the study period.

(38% v. 30%) follow-up visits was statistically significantly higher for the HIV-positive women (Figure 1). Cause and confirmation of death could be accurately determined in 20 women in the total study population.

HIV status and change in quality of life over the study period

The domains of dyspnoea, financial difficulties, lymphoedema and menopausal symptoms remained unchanged during the study period. HIV-positive women experienced no improvement in insomnia, appetite loss, nausea and vomiting, diarrhoea, social role or any of the sexual domains over the study period. In contrast, HIV-negative women experienced statistically significant improvement in all sexual domains other than sexual/vaginal function. The improvement in QOL of HIV-negative women was statistically significantly more than their HIV-positive counterparts in all domains, with the exception of

TABLE 2: Change in quality of life during study period.

Quality of life domain	HIV- <i>n</i> = 173	HIV+ <i>n</i> = 48	HIV- versus HIV+
Physical function	<i>p</i> < 0.01†	<i>p</i> < 0.05†	<i>p</i> < 0.05
Role function	<i>p</i> < 0.01‡	<i>p</i> < 0.01‡	NS
Dyspnoea	NS	NS	NS
Pain	<i>p</i> < 0.01‡	<i>p</i> < 0.01‡	<i>p</i> < 0.01
Fatigue	<i>p</i> < 0.01‡	<i>p</i> < 0.01‡	<i>p</i> < 0.01
Insomnia	<i>p</i> < 0.01‡	NS	NS
Appetite loss	<i>p</i> < 0.01†	NS	<i>p</i> < 0.01
Nausea and vomiting	<i>p</i> < 0.01‡	NS	<i>p</i> < 0.01§
Constipation	<i>p</i> < 0.01†	<i>p</i> < 0.05†	NS
Diarrhoea	NS	NS	<i>p</i> < 0.01
Cognitive function	<i>p</i> < 0.01‡	<i>p</i> < 0.05‡	<i>p</i> < 0.01
Emotional role	<i>p</i> < 0.01‡	<i>p</i> < 0.01‡	<i>p</i> < 0.05
Social role	<i>p</i> < 0.01†	NS	<i>p</i> < 0.05
Financial difficulties	NS	NS	NS
Global health status	<i>p</i> < 0.01†	<i>p</i> < 0.01†	<i>p</i> < 0.01
Symptom experience	<i>p</i> < 0.01‡	<i>p</i> < 0.05‡	<i>p</i> < 0.01
Lymphoedema	NS	NS	NS
Peripheral neuropathy	NS	<i>p</i> < 0.01‡	<i>p</i> < 0.01
Menopausal symptoms	NS	NS	NS
Body image	<i>p</i> < 0.01†	<i>p</i> < 0.01†	<i>p</i> < 0.05
Sexual worry	<i>p</i> < 0.01‡	NS	NS
Sexual activity	<i>p</i> < 0.01†	NS	NS
Sexual/vaginal functioning	NS	NS	<i>p</i> < 0.01
Sexual enjoyment	<i>p</i> < 0.05†	NS	<i>p</i> < 0.01

NS, not significant.

†, Improved; ‡, decreased; §, HIV+ > HIV-.

All other *p* values in column HIV- > HIV+.

role function, insomnia, constipation, sexual worry and sexual activity (Table 2). Global health improved in both groups, with HIV-negative women experiencing a greater improvement. PN did not change in HIV-negative women but HIV-positive women experienced an initial decline in this symptom at post treatment with a return to pretreatment values at the 3-month follow-up visit. The change in PN was statistically significantly different between HIV-negative and HIV-positive women.

Discussion

The results of the study show significant demographic differences between HIV-positive and HIV-negative women with a diagnosis of cervical cancer. The former group is statistically younger, and has a higher educational level and higher unemployment rate than the latter. Black women have a statistically higher HIV-positivity rate than mixed race and white women. Single women had the highest HIV-positivity rate. Monthly income is similar in both groups. RT was more frequently used than CR in HIV-positive patients. The 22% HIV-positive rate in the current study is higher than previously reported rates. This change is the result of a general change in HIV-positive rates in the total population over time.² Black women had a higher HIV-positive rate than mixed race or white women. A previous study documented a higher incidence (30%) of positive syphilis serology amongst black women with cervical cancer than in their white and mixed race counterparts.¹² The younger age of HIV-positive cervical cancer patients confirms previous studies of HIV in cervical cancer cases. In previous studies, the difference in mean age between

HIV-negative and HIV-positive patients was reported as 10 years, whilst the current study shows a 7-year age difference.^{5 13 14} The stage distribution in the current study was similar in HIV-negative and HIV-positive women. Despite the similar stage distribution, significantly more HIV-negative than HIV-positive women received CR. The selection by the presiding clinician of the inability of HIV-positive women to tolerate the chemotherapy because of low CD4 counts, gave rise to this difference.

The majority of QOL domains in HIV-negative women improved with treatment with prolonged effect up to 3 months' follow-up. Improvement of QOL domains in HIV-positive women was statistically less than in HIV-negative women. PN domain did not change in HIV-negative women. In HIV-positive women, initial improvement occurred in PN with relapse to pretreatment level at 3 months. Appetite loss in HIV-positive women initially improved after treatment and returned to pretreatment levels at 3 months' follow-up. HIV-negative women showed an improvement in appetite loss up to 3 months' follow-up. The QOL of HIV-negative women significantly improved in the majority of domains. HIV-positive women had fewer domains improved by treatment, and the magnitude of improvement was less than that amongst HIV-negative women. Temporary improvement of pain, fatigue and appetite loss after treatment in HIV-positive women reverted to pretreatment levels at 3 months' follow-up. Pain and fatigue are AIDS-related conditions that are prevalent in AIDS patients, despite adequate treatment. Depression is associated with these symptoms, and the difference in emotional functioning in the current study underlines the element of depression in the HIV-positive women.¹⁵ The AIDS-related impact on QOL accounts for these relapses in QOL domains. Diarrhoea was significantly more in HIV-positive women than in HIV-negative women, and treatment did not change the incidence in either group. Diarrhoea is commonly associated with AIDS and can have numerous causes, both infectious and non-infectious, for example AIDS medication-related gastro-intestinal side-effects.¹⁶ Constipation improved in both HIV-negative and HIV-positive women. Radiation is associated with increased stool frequency owing to radiation-induced mucosal rectal damage. PN paradoxically improved in both groups after treatment and reverted to pretreatment levels in HIV-positive women. Contrary to expected cisplatin-related toxicity, treatment did not result in an increase of PN. The dose of cisplatin, which did not reach the cumulative threshold dose > 250 mg - 350 mg/ m², may explain the absence of PN. Cisplatin-associated PN may occur up to 8 months after exposure, and therefore longer follow-up may reveal PN.¹⁷

In the present study, higher rates of loss to follow-up occurred in HIV-positive women. A meta-analysis of sub-Saharan low- and middle-income countries' antiretroviral treatment programmes reports on causes of loss to follow-up. Self-transferring care to other facilities (18.6%), unreported death (38.8%) and stopping treatment were identified as the major reasons for loss to follow-up.¹⁸

WHO AIDS stage 3 and 4 cases have a mortality rate of 72.12 per 100 person-years in the first 6 months after initiation of treatment. The mortality rate decreases to 7.9 per 100 person-years after 12 months.¹⁹ The mortality rate is compounded by cervical cancer-related death. In a South African study, the mortality rate after treatment of stage III cervical cancer was the highest in the first 6 months after treatment.¹² In Kenya, a 41% loss to follow-up occurred in women receiving treatment for cervical cancer.²⁰ Tracking of women after missed appointments is not done routinely owing to resource constraints.¹⁸ Verifying HIV-related deaths by checking death certificates is subject to 90% misclassification of HIV deaths in South Africa.²¹

Limitations of the present study include a short follow-up subsequent to completion of therapy. The short follow-up limits the conclusion to long-term effects of treatment. Prolonged follow-up may reveal an increased incidence of PN. The higher loss to follow-up rate of HIV-positive women during the study period precludes sub-analysis of smaller groups, for example treatment-related PN in those women undergoing CR.

In conclusion, the study documents the demographic difference in HIV-negative and HIV-positive women with cervical cancer with regard to a younger age in the latter group. The 5-year survival benefit of CR in comparison with RT in HIV-negative women with stage III to IVA is a statistically non-significant 3%.⁶ The poor response of HIV-positive women to CR raises the question of whether CR is appropriate in these circumstances.⁵ A significant difference exists in the short term in certain QOL domains of HIV-positive women with cervical cancer receiving RT or CR. In these circumstances, the different impact on long-term QOL of HIV-positive women with cervical cancer receiving RT or CR warrants further study.

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Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions

G.d.T. (Stellenbosch University) was the project leader and designed the study, wrote the protocol, collected the data and wrote the paper. M.K. (Stellenbosch University) performed the statistical analysis and contributed to discussions. Both authors read and approved the manuscript.

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Chapter 6. The contextual QOL of cervical cancer survivors: A cross-sectional study of QOL 18 months after completing therapy

Introduction

Cervical cancer remains a significant health problem with almost half a million women diagnosed each year, and 200 000 annual deaths reported worldwide. In developing countries, effective cervical cancer screening and appropriate treatment decreases the rate of advanced cervical cancer and increases survival.⁽¹⁾ Based on five randomised trials resulted in the National Cancer Institute to suggested in 1999 platinum-based concurrent chemoradiation as first-line treatment for patients with locally advanced stage cervical cancer.⁽²⁻⁶⁾ A systemic review and meta-analysis of 19 trials between 1980 and 2000, comprising of 458 patients, has shown a significant survival benefit with chemoradiation in comparison to radiotherapy radiation therapy. A five-year survival benefit of 12% increase with chemoradiation was documented.⁽⁷⁾ Trials included in this review was heterogeneous with regards to selection criteria, the cytotoxic agent used and treatment regimes. Different treatment regimens in the control arms complicated the interpretation of survival benefits. From these limitations, it is evident that an individual patient data analysis would be required to define survival benefits clearly. An individual patient data analysis, including 15 trials, was performed. The individual patient data study concluded that chemo radiation added a 6% survival benefit in comparison to radiation therapy. A decrease survival benefit, with increasing stage, was documented. Absolute survival benefits of 10 % (stage IA-IIA), 7% (stage IIB) and 3% (stage III-IVA) were documented. The 3% survival advantage of chemo radiation in stage III-IVA must evaluated in the context of the impact on QOL due to the addition of chemotherapy. The individual patient data analysis concluded that data on long-term side-effects of chemo radiation and its impact on QOL are lacking.⁽⁸⁾

The QOL of cervical cancer survivors is the result of the disease related, patient-related and medical factors. The concept of health related contextual QOL, as described by Ashwing-Giwa, creates a framework that incorporates factors such as cultural and socioeconomic circumstances. Contextual factors impacting on QOL are language barriers, socioeconomic status and difficulties in accessing health care. Ethnic variations exist in the QOL. Socioeconomic status is a further determinant in the QOL. These factors are relevant to prevailing South African socioeconomic factors. Socioeconomic stress is an important factor influencing physical and mental QOL.^(9,10)

South Africa has a high prevalence of HIV -positive individual (18%) in the population.⁽¹¹⁾ The concomitant HIV infection and cervical cancer further compromise health and impacts on treatment. The selection of treatment may influence QOL. Cervical cancer and AIDS are associated diseases. The Centres for Disease Control and Prevention identifies cervical cancer as an AIDS-defining condition. Cervical cancer is an AIDS stage IV disease in the World Health Organization clinical staging of the condition.^(12,13) HIV-positive women with cervical cancer present in more advanced stage than HIV -negative cases. Human immune deficiency virus - positive women tolerate chemotherapy, as part of chemo radiation, poorly, and their prognosis are compromised.⁽¹⁴⁾ Quantitative data on the impact of chemo radiation on the QOL in HIV - positive cervical cancer survivors is lacking.

6.1.1 Review of QOL research in cervical cancer survivors.

6.1.1.1 Demographics

Table 1. Demographic details of the articles of cervical cancer survivors and QOL (*=Not Available)

Country	n	Mean age(years)	Stage I and II (%)	High Income (%)	Illiterate (%)	Mean survival (years)
South Korea(15)	860	NA*	85.2	77.1	4.2	5.86
Germany(16)	121	47.8	98.3	NA*	0	0.6
USA(17)	41	53.3	87.8	46.3	9.8	1-20
Japan(18)	60	61.4	50	NA*	0	2.5
Netherlands(19)	291	53	86	NA*	0	6.6
Hong Kong(20)	173	54.8	85	NA*	15.6	2.4
USA(10)	560	48.5	83.6	39.4	NA*	3.29
14 Countries(21)	346	49.7	80.7	NA*	1.4	NA*
Poland(22)	157	NA*	43.9	NA*	0.64	0.5
France(23)	173	56.1	91	22.7	0	5-10

The available research on the QOL of cervical cancer survivors is from first world countries (Table 1). Stage I is the predominant stage in all reported studies. Stage distribution in developing countries, for example, South Africa, reflects the converse with 70% patients presenting with advanced stage.⁽²⁴⁾ The stage at presentation influences the QOL of the patients.

The subsequent treatment, related to the stage, has a further influence on the QOL. Based on five randomised trials resulted the National Cancer Institute to suggested in 1999 platinum based concurrent chemo radiation as first-line treatment for patients with locally advanced stage cervical cancer.^(2-5,25,26) A systemic review and meta-analysis of 19 trials between 1980 and 2000, comprising of 458 patients, has shown a significant survival benefit with chemo radiation in comparison to radiotherapy radiation therapy. A five-year survival benefit of 12% increase with chemo radiation was documented.⁽⁷⁾ Trials included in this review was heterogeneous with regards to selection criteria, the cytotoxic agent used and treatment regimes. Different treatment regimens in the control arms complicated the interpretation of survival benefits. From these limitations, it is evident that an individual patient data analysis would be required to define survival benefits clearly. An individual patient data analysis, including 15 trials, was performed. The individual patient data study concluded that chemo radiation added a 6% survival benefit in comparison to radiation therapy. A decrease survival benefit, with increasing stage, was documented. Absolute survival benefits of 10 % (stage IA- IIA), 7% (stage IIB) and 3% (stage III-IVA) were documented. The 3% survival advantage of chemo radiation in stage III-IVA must evaluated in the context of the impact on QOL due to the addition of chemotherapy. The individual patient data analysis concluded that data on long- term side-effects of chemo radiation and its impact on QOL are lacking.⁽⁸⁾

6.1.1.2 Results of QOL studies in cervical cancer survivors

A review of QOL research of long-term cervical cancer survivors for the period 1966 to 2005 identified 23 studies. After qualitative evaluation, eight studies with sound methodology were analysed. The review identified limitations of available research as methodological problems related to small sample size, the use of invalidated questionnaire and that the majority of studies did not correct for confounding variables, for e.g. age, stage of disease and treatment

modalities. These limitations emphasize the in cooperation of contextual factors in future QOL research. The studies with good methodology focused primarily on sexual and social function after treatment, and less on physical and psychological well-being. The trend was that radiotherapy was more associated with reduced QOL dimensions than surgery or chemotherapy. In earlier stages of cervical cancer and following surgery alone, there seem to be minor differences between cervical cancer survivors and healthy control groups of the general population concerning various QOL domains.⁽²⁷⁾

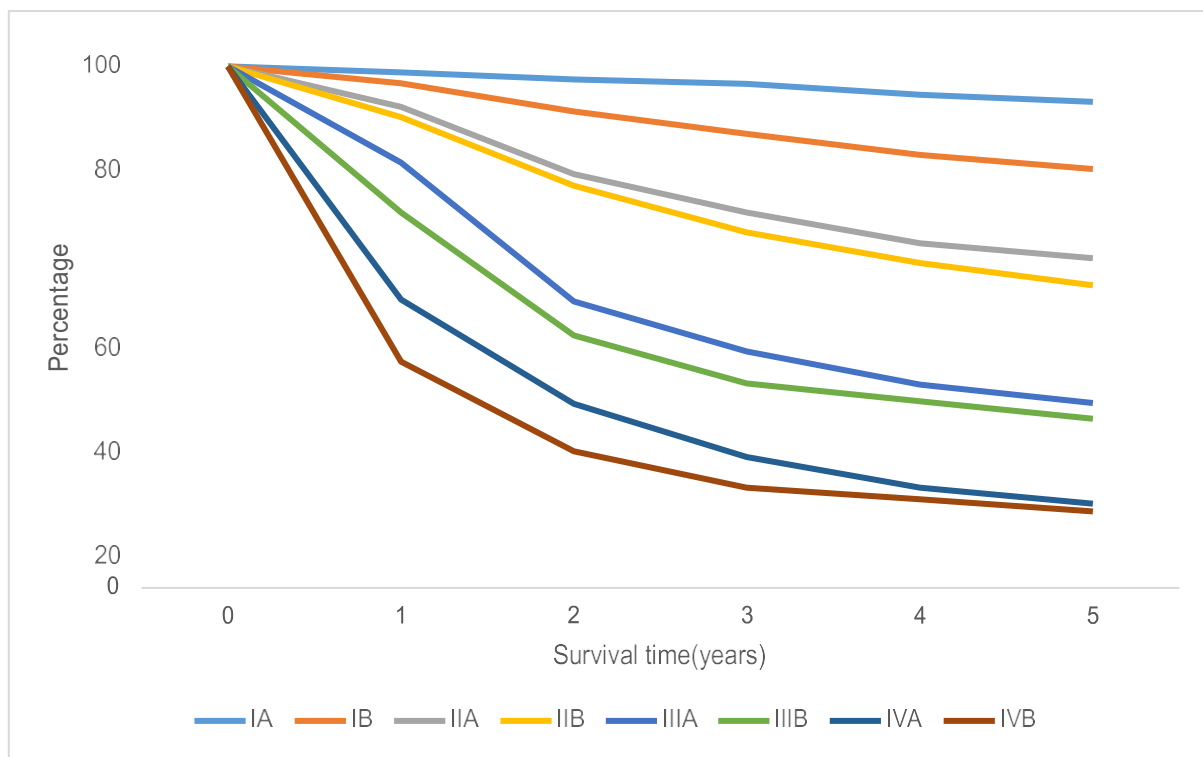
A second review for the period 2005-2009 identified 26 quantitative and five qualitative studies. This review organised the findings of research according to the contextual model of QOL. Medical factors identified impacting on QOL were age, stage of disease and treatment modalities. The systemic, non-medical factors, which influenced the QOL were social, ecological and cultural factors.⁽²⁸⁾

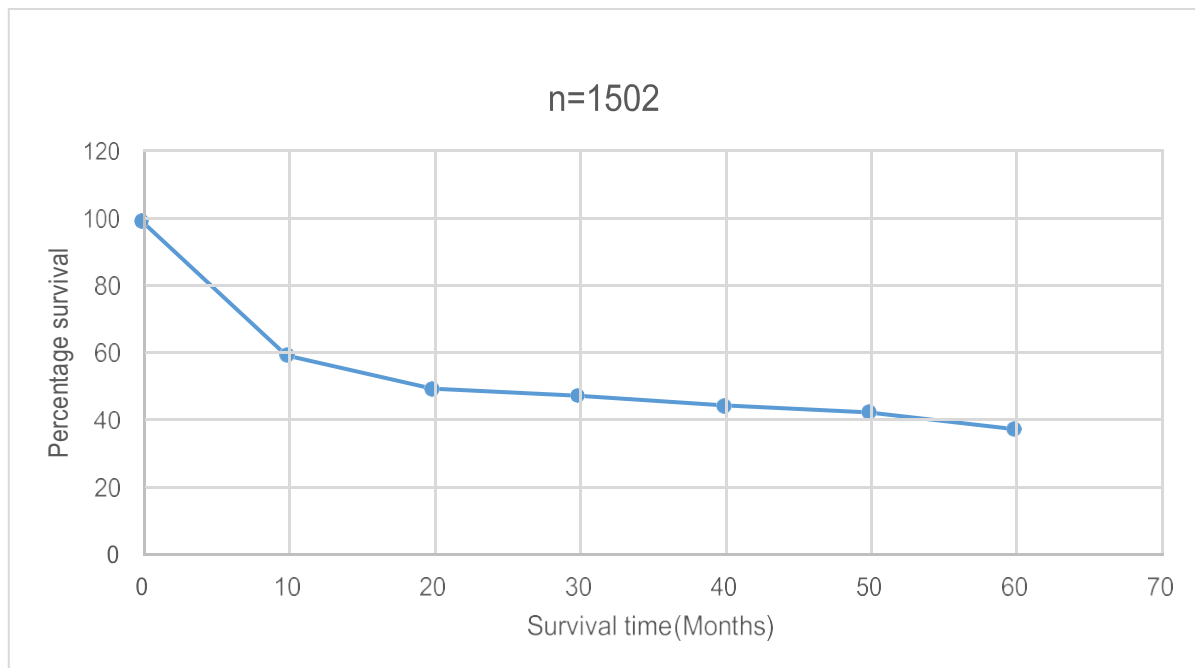
Regarding age-specific factors, for example, young cervical cancer survivors reported more reproductive concern than their healthy controls. In Chinese cervical cancer survivors, social relationships deteriorated with age. Advanced stage disease reported worse scores than early-stage disease in physical functioning.⁽²⁰⁾ In a French study treatment, related effects on QOL are reflected by a significant decrease of QOL in physical and sexual domains related to radiation therapy as primary treatment or in combination with surgery and chemotherapy.⁽¹⁹⁾ Socioecological circumstances resulting in decreased QOL amongst cervical cancer survivors were unemployment, low education levels, and low socio-economic status. Social rejection of Chinese cervical cancer survivors reflects the cultural influence on the QOL. In Chinese societies, cervical cancer is socially stigmatised due to the connection of sexually transmittable disease, multiple sexual partners, and early coitarche. This rejection resulted in Chinese women to experience self-blame and reduction in emotional well-being.⁽²⁰⁾ The second review concluded that the future QOL studies should use the contextual model of QOL.⁽²⁸⁾

6.1.2 Definition of cervical cancer survivors.

In cervical cancer survivors, the timing of cross-sectional QOL research is influenced by the survival pattern of the study population and the stage of the disease determines the survival curve. The survival curves of a total of 15070 cases of cervical cancer, from 2000-2002, in the United States of America is depicted in Graph 1. The survival curve of the stage I cases shows a gradual decline over five years.⁽²⁹⁾ In comparison, survival curves in stage III-IV shows an initial sharp decline in the first two years and then the survival curve levels off. Survival analysis of 1502 cases of stage III cervical cancer at Tygerberg Hospital document that 80% of all deaths occur within the first 18 months after diagnosis as depicted in Graph 2. QOL assessment beyond 18 months would be reflective of cervical cancer survivors in this population.⁽²⁴⁾

Graph 1. Cervical cancer survival figures from the United States of America (USA) 2000-2002 (N=15070).



Graph 2. Survival figure of stage III cervical cancer at Tygerberg Hospital

6.1.3 Aims of the study

The aims of the study were:

- (1) Describe the demographics and QOL in cervical cancer survivors in a population with high incidence of advanced stage cervical cancer.
- (2) Determine the effect of contextual factors e.g. age, race, education, income, stage, and treatment and human immune deficiency virus status on the QOL of cervical cancer survivors.
- (3) Determine the possible difference in the QOL patients receiving chemoradiation or radiation therapy.

6.2 Methods and materials

6.2.1 Inclusion criteria

Patients attending the Unit of Gynaecologic Oncology at Tygerberg Hospital for routine follow-up, after previous treatment for cervical cancer, were approached to participate in the study. The unit is one of two tertiary referral units for the public-sector patients of the Western Cape. The Western Cape has a population of 5.8 million. The majority of the population (85%)

does not have private insurance and is dependent on the public facilities provided at the two tertiary hospitals (Tygerberg Hospital and Grootte Schuur Hospital) for treatment of invasive cervical cancer. ⁽³⁰⁾ Women presenting for routine follow-up at the unit were approached for enrolment. Patients were eligible if they had previously histologically proven cervical cancer and had received treatment at Tygerberg Hospital. The patients provided informed consent and completed the questionnaire in the language of the choice e. g isiXhosa, English or Afrikaans. ⁽³¹⁾ A research assistant aided illiterate patients. To exclude bias, the research assistant had no medical background and was not involved in the clinical management of the patients. Inclusion in this study required a period of 18 months after the completion of treatment. Ethical approval was obtained from the local committee (N13/02/020). Relevant clinical data were extracted from the clinical records.

6.2.2 Questionnaires

The European Organisation for Research and Treatment of Cancer (EORTC) QOL Core Questionnaire (EORTC QLQ-C30) and the Cervix Cancer Module (QLQ-CX24) were used to assess QOL. The EORTC QLQ-C30 consists of 30 items comprising five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea/vomiting, and pain), the overall QOL scale, and 6 single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The EORTC QLQ-C30 was analysed according to the procedures recommended by the EORTC QOL Group. ⁽³²⁾ Higher scores on the QLQ-C30 functioning scales and the overall QOL scale indicate a higher level of functioning and better QOL. Higher scores on the symptom scales or single item scales represent a higher level of symptoms or problems. The EORTC QLQ-CX24 module includes three multi-item scales (Symptom Experience, Body Image, and Sexual Functioning) and five single item scales (lymph oedema, lower back pain, menopausal symptoms, tingling and

numbness, and sexual enjoyment). The higher scores are equivalent to worse or more symptoms except for items 49 and 54 (higher score indicates better QOL).⁽³³⁾

6.2.3 Statistical analysis

Descriptive statistics are used to characterise the study sample regarding the contextual factors of socio-demographic and medical variables. Univariate analysis is used to assess the influence of the contextual factors on the QOL domains. Means were compared with the Student's t-test. The Student's t-test is a method of testing hypotheses about the mean of a small sample drawn from a normally distributed population when the population standard deviation is unknown. Spearman and Pearson's correlation coefficients were calculated to evaluate the relationship between the independent contextual factors and the dependent quality-of-life domains. Chi-square tests were used for categorical data. A p-value of $p < 0.05$ was significant and $p < 0.01$ as highly significant. Multiple regression analysis was performed to determine the predictive value of the contextual factors as independent variables on the various quality-of-life domains as the dependent variables. Statistical analysis was carried out with the use of STATISTICA R version 12 software.

6.3 Results

6.3.1 Demographic data

A total of 106 women enrolled in the study between 01/07/2013-29/01/2014. The education level shows 8% of women to be illiterate. Illiterate status is defined as the inability to read and write. These women received assistance in the completion of the questionnaires. Educational levels reflect the 37.7% of the study group finished grade seven successfully. A further 9% completed their high school career successfully (Graph 3). The majority of household incomes were below the poverty line of ZAR3500 per month. Seventeen percent of women had no monthly income (Graph 4). Advanced stage disease (stage III/IV) comprised 45.3% of the study with stage III the commonest stage at 40.6 % (Graph 5).

Table 2. Demographic data of the study group (n=106).

Characteristics	Outcome
Age(years)	55 $\overline{\pm 10.2}$ (35-78)
Education level (%)	
Illiterate	8
Some primary education	45
Some secondary education	37
Race (%)	
Coloured	77
Black	17
White	6
Income(ZAR)	1957 $\overline{\pm 2027}$ (0-10367)
Marital state (%)	
Single	36
Married	40
Widow	13
Divorce	11
Stage (%)	
I	23

II28

III41

IV5

Special category	4
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Treatment (%)

Surgery	17
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Radiotherapy	22
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Chemo radiation therapy	56
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Combination modalities	5
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Employment (%)

Employed	33
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Pension	13
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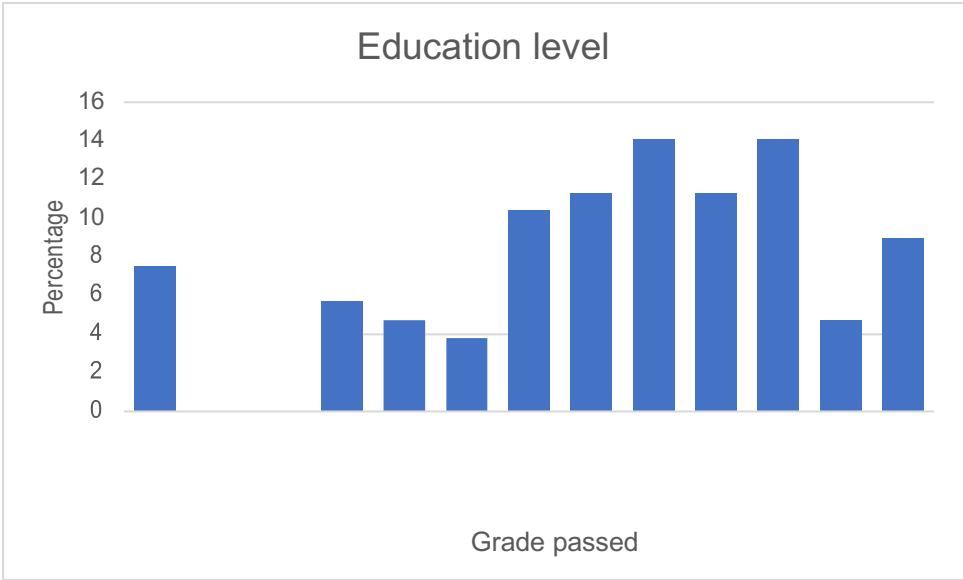
Unemployed	58
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Human immune deficiency virus positive (%)	9
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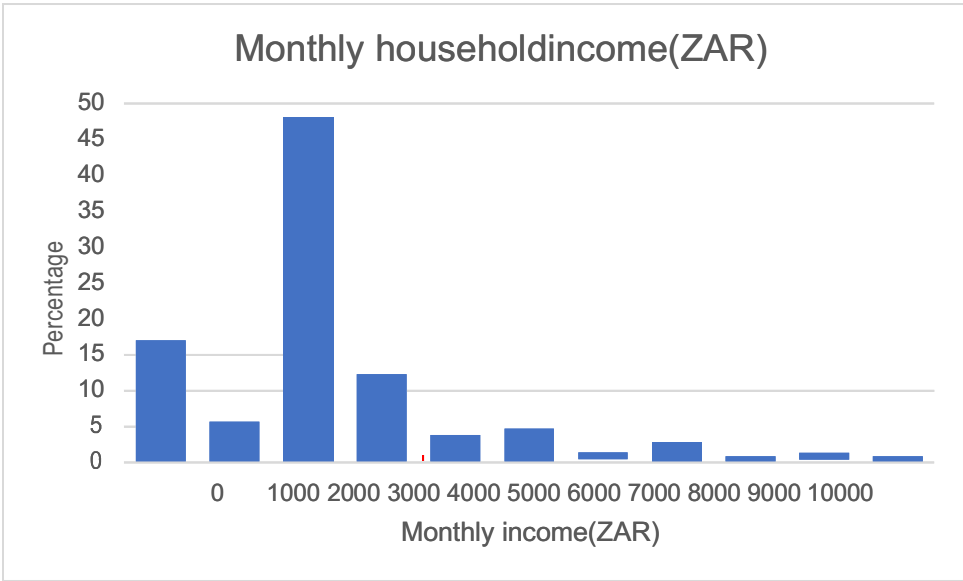
Majority of cases were coloured women and the human immune deficiency virus -positive prevalence was 9%. Human immune deficiency virus-positive women had a mean age of 50.5 years versus human immune deficiency virus-negative women 55.5 years ($p=0.14$). No differences were present between HIV -positive and HIV-negative patients with regards to educational level, income level, stage distribution, marital status, and treatment or employment status. A significant difference of HIV-positive status between the different race groups was

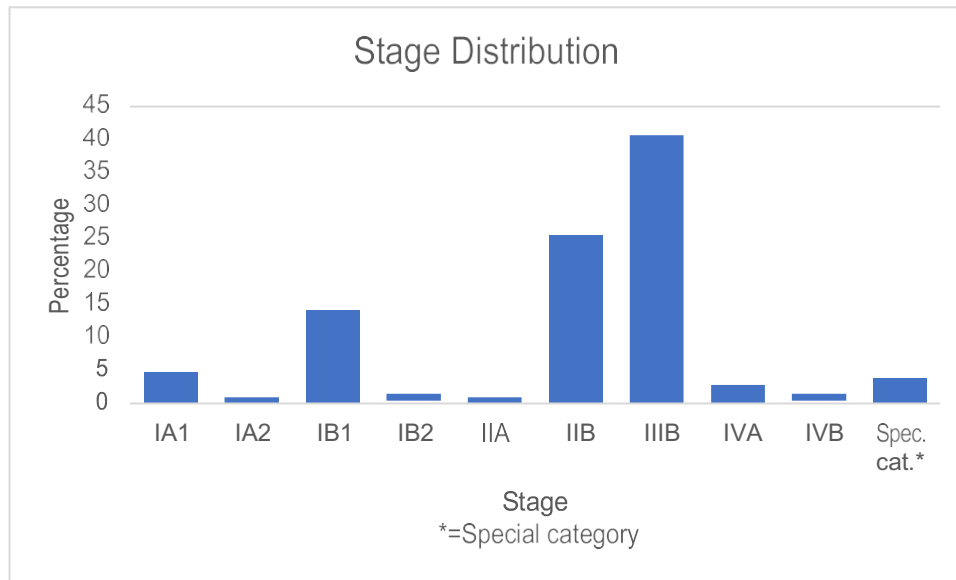
documented with human immune deficiency virus-positive status of blacks (33%) coloured (4%) and white (17%) (p=0.02) Table 2.

Graph 3. Education levels



Graph 4. Monthly income (Redline=poverty line)



Graph 5. Stage distribution

6.3.2 Univariate analysis of contextual factors.

The influence of contextual factors of age, race, marital status, education level, employment status, stage of disease, treatment and HIV status were analysed using univariate analysis.

Increased age decreased sexual activity ($p < 0.01$). Black and coloured women experienced better social functioning and body image than their white counterparts ($p < 0.01$). Black and white women had less financial difficulties than mixed ethnicity women ($p < 0.01$). Married women had more sexual worry than divorced, single or widowed women ($p < 0.01$) but had higher sexual activity ($p < 0.01$). Educational level did not significantly influence any QOL domain. Unemployment decreased sexual activity ($p < 0.01$) and physical functioning ($p < 0.01$). Advanced stage and non-surgical treatment resulted in decreased sexual activity ($p < 0.01$). HIV-positive women had a lower emotional role ($p < 0.01$) and sexual/vaginal functioning ($p < 0.01$) (Table 3).

Table 3. Univariate analysis of QOL domains significantly influenced by contextual factors as reflected by p-values.

	Age	Race	Marital status	Employ ment	Stage	Treatment	HIV Status
Physical function	0.18	0.9	0.93	<0.01	0.05	0.11	0.98
Emotional role function	0.05	0.1	0.3	0.07	0.16	0.6	<0.01
Social role function	0.27	<0.01	0.12	0.98	0.91	0.8	0.16
Financial difficulties	0.24	<0.01	0.23	0.2	0.04	0.77	0.19
Body Image	0.35	<0.01	0.1	0.72	0.75	0.66	0.67
Sexual Worry	0.49	0.7	<0.01	0.49	0.4	0.13	0.38
Sexual Activity	<0.01	0.6	<0.01	<0.01	<0.01	<0.01	1
Sexual/Vagina l Functioning	0.56	0.9	0.99	0.09	0.61	0.72	<0.01

6.3.3 Multiple regression analysis prediction of QOL.

Race, marital status, employment status and HIV status predicted quality-of-life domains using multiple-regression analysis. Race predicted dyspnoea($p=0.01$) and financial difficulties($p=0.00$). Marital status predicted both role ($p=0.03$) and social functioning ($p=0.04$). Employment status predicted physical functioning ($p=0.04$), fatigue ($p=0.04$),

cognitive functioning ($p=0.02$) and global health status ($p=0.04$). Race ($p=0.01$) and HIV positive status ($p=0.04$) predicted increased dyspnoea. (Table 4).

Table 4. Multiple regression results of contextual factors on QOL domains.

	Race		Marital status		Employment		HIV-status	
	p-value	B	p-value	β	p-value	B	p-value	B
Physical	0.66	-0.05	0.76	-0.12	0.04	-0.30	0.85	-0.02
Role	0.60	-0.06	0.03	-0.23	0.84	-0.06	0.49	-0.50
Dyspnoea	0.01	0.32	0.78	-0.06	0.14	-0.04	0.04	0.23
Fatigue	0.59	0.06	0.46	-0.04	0.04	-0.26	0.20	0.15
Cognitive	0.38	-0.10	0.90	-0.05	0.02	-0.42	0.95	0.10
Social	0.65	-0.01	0.04	-0.29	0.91	-0.01	0.56	0.07
Financial difficulties	0.00	-0.42	0.29	-0.15	0.40	0.08	0.16	-0.15
Global health	0.67	0.05	0.35	-0.28	0.04	-0.07	0.11	0.18

6.4 Discussion

6.4.1 Demographics of the study group.

The current study's demographics document cervical cancer survivors at Tygerberg Hospital, South Africa, as poorly educated, middle-aged women with low income. The mean age of 55 years the current study contrasts with reported South Korean (49,9 years) and Chinese (43,2 years) of cervical cancer survivors(34,35). The advanced stage (stage III/IV) percentage of

cervical cancer survivors in the current study is 46%. The corresponding figure from Taiwanese studies reports 6% advanced stage.⁽³⁶⁾ High mean age and high incidence of advanced stage in the current study is the result of a resourced constraint country without cervical screening. In the absence of screening early asymptomatic stage cervical cancer is not diagnosed and more advanced stage distribution follows. In the current study, the mean age of 55 years of cervical cancer survivors is the result of the predominance of advanced stage. The mean age of Stage III cervical cancer in a resourced country is 55 years.⁽³⁷⁾ The advance stage represents 46% of cervical cancer survivors and this contrasts with 70% of advanced cervical cancer at diagnosis. This difference is attributable to the attrition due to death of the advanced cases before 18 months post-treatment.

The current study documents a mean household income ZAR1957, which is below the poverty line of ZAR3500 per household as defined by the Western Cape Provincial Government. The poverty line is an income defined, in terms of local conditions and cost of living, to sustain life. Poverty figure for the Western Cape Province is 34.9% of the population. In the current study, 86% of household had an income below ZAR3500. A further indicator of poor socioeconomic conditions is the unemployment rate. The unemployment rates in the Western Cape Province is 22.2%.⁽³⁰⁾ The current study population has an unemployment rate of 54%. The unemployment contributes to the poor household income. Yoo et al describe a 20.5 % unemployment amongst South Korean cervical cancer survivors. This correlates with unemployment at diagnosis. Concomitant low education leads to a poor socioeconomic status.⁽³⁸⁾ The low socio-economic, as reflected by poor education and low-income rate of the current study group confirms previously reported studies describing advanced cervical cancer as a disease of low socioeconomic women.⁽²⁰⁾

6.4.2 Influence of contextual factors on the quality of life

The study identifies race, marital status, employment and HIV status as significant factors, predictive in the QOL of long-term cervical cancer survivors. The sexual domains (sexual worry, sexual activity, sexual/vaginal functioning and sexual enjoyment) of QOL were significantly influenced by contextual factors. A decrease in sexual activity was related to low income, unmarried state, advanced stage of disease and treatment. There was no difference in the QOL between patients in the radiation therapy and chemoradiation groups.

Age-related decline in sexual activity occurs in healthy populations and thus is expected in cervical cancer survivors. In the current study, the mean age of 55 years falls in the menopausal age with associated urogenital atrophy that could result in the reported decrease in sexual activity that is unrelated to cervical cancer and its treatment. This is substantiated by Lee et al. Their study compared QOL and sexuality between cervical cancer survivors and healthy women. The mean age in this study was 47 years and there was no difference in sexual activity between the two groups.⁽³⁴⁾

The race was a predictor of increased dyspnoea and increased financial difficulties. The race associated increase in dyspnoea could be the result of HIV associated lung infections in black women who had a significantly higher incidence of HIV. Prevailing discrepancies in financial status between the race groups in the Western Province serves as an explanation to the racial difference encountered with regard to financial difficulties by the various races and is unrelated to cervical cancer.

Married women experienced an increase in sexual worry but had higher sexual activity than their divorced, single or widowed counterparts. Marital state predicted improved role and social function. The correlation between married women and increased sexual function is also identified in Chinese women.⁽³⁵⁾ The stability of marriage provides the backdrop for cervical cancer survivors to improve social and role function.

Unemployment contributes to poor income and decrease in socioeconomic status. This resulted in a decrease in sexual activity and decreased physical functioning. The current study confirms previous studies showing a decrease in physical function related low socioeconomic circumstances. Life burden remains a significant predictor of QOL.⁽³⁸⁾

Advanced stage and associated treatment resulted in decrease sexual activity. Radiation and chemo radiation therapy used in advanced stage result in vaginal dysfunction to fibrosis dryness and atrophy. No difference in the decrease in sexual activity or sexual /vaginal function were noted between radiation or chemo radiation therapy.

In the current study, HIV-positive status did not reduce sexual activity but was associated with decreased sexual/vaginal functioning. Emotional role functioning was significantly decreased in HIV-positive women. Peripheral neuropathy complaints were not increased in HIV-positive women. HIV infection results in peripheral neuropathy. The treatment with anti-retroviral therapy, specifically didanosine, zalcitabine, and stavudine, increases the incidence of peripheral neuropathy.⁽³⁹⁾ To these existing factors the addition of cisplatin, known to cause peripheral neuropathy, as part of chemoradiation, may increase peripheral neuropathy.⁽⁴⁰⁾ The absence of peripheral neuropathy in the current study could be explained by the 18 months since cisplatin treatment, allowing for recovery. The appropriateness of chemo-radiation therapy in AIDS patients with advanced stage cervical cancer has been questioning as it confirms a three percent survival benefit in comparison to radiation therapy.⁽¹⁴⁾

The limitations of the current study are that it mainly involved patients of a geographically distinct origin. The geographical area has a racial composition and socioeconomic status that would not apply to other regions. A further limitation in the current study includes a low incidence of HIV-positive cervical cancer survivors. These low numbers do not allow to differentiate between the possible difference in the QOL between radiation therapy and

chemoradiation therapy. This may influence the findings on treatment-related QOL domains e.g. peripheral neuropathy.

6.5 Conclusion

Cervical cancer survivors in the current study are women from low socioeconomic status with associated low education and income levels. Sexual domains of QOL are the domains, which are most commonly influenced by multiple contextual factors. No difference in the QOL between radiation therapy and chemo-radiation therapy could be demonstrated. HIV-status did not impact significantly on the QOL. The importance of reporting the contextual QOL in future studies is demonstrated.

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Chapter 7. Qualitative research and cervical cancer: prevention, diagnosis, and treatment.

7 Introduction

Qualitative research is a multi-disciplinary paradigm used in social and natural sciences. It originated in social sciences. Major approaches to qualitative research include a) ethnography (drawn from anthropology); b) phenomenology (drawn from philosophy) and c) grounded theory (drawn from sociology). Typically, the research questions addressed by qualitative methods are discovery-oriented, descriptive and exploratory in nature. Qualitative researchers gather an in-depth understanding of human behaviour and the reasons that govern human behaviour. Various aspects of behaviour are based on deeply held values, personal perspectives, experiences and contextual circumstances of both researcher and study subjects. The subjective nature of the research results in criticism on the reproducibility and thus scientific validity.⁽¹⁾ The qualitative research investigates the ‘why’ and ‘how’ of decision making, not the ‘what, where, and when’ as in a quantitative research. Therefore, the need is for smaller, focused samples rather than larger random samples. Qualitative analysis involves categorising data into patterns (themes) as the primary basis for organizing and reporting results. Qualitative researchers rely on several methods for gathering information: (1) interviews of participants in a setting, (2) direct observation, (3) in-depth interviews, (4) focus groups, and (5) analysis of documents and materials.⁽¹⁾

It is common to draw a value based distinction between qualitative and quantitative research as scientific investigations. Opinions exist that these methods are in conflict. Denzin argues that evidence-based gold standards applicable to quantitative research e.g. Cochrane and Campbell criteria, experimental methodologies, randomized control trials poses a threat to qualitative research. He states that funding and acceptance of publications of qualitative are detrimentally affected by the application of these standards. He articulates his views as follows:

”Standards for assessing quality research are pedagogies of practice, moral, ethical and political institutional apparatuses that regulate and produce a particular form of science, a form that may be no longer workable in a trans-disciplinary, global and postcolonial world. Indeed, within the evidence-based community, there is the understanding that qualitative research does not count as research unless it is embedded in a randomized control trial (RCT)! Further, within this community, there are no agreed-upon procedures, methods, or criteria for extracting information from qualitative studies.”^(2,3)

Fielding responds with a different perspective:

“Qualitative researchers are represented not only on sociology panels but in education, socio-legal studies, social policy, criminology, law, health studies (subjects allied to medicine), sport science, dance and theatre studies, and even psychology. Plenty of qualitative work was rated highly, including work in Denzin’s preferred non-foundationalist/feminist and communitarian vein.”⁽⁴⁾

Qualitative studies, as a cross-disciplinary research method, address societal issues on a comprehensive basis, including health-related problems. In research, a mixed-methods approach (a combination of qualitative and quantitative techniques) is often used. Qualitative research is, in some cases, instrumental to developing an understanding of a phenomenon as a basis for quantitative research. In other cases, it can inform or enrich the understanding of quantitative results. Similarly, quantitative research may inform, or be drawn upon in the process of qualitative research. ⁽¹⁾ Quantitative research results are represented by numerical figures and tables, and qualitative by descriptive findings illustrated by direct quotations of the subjects in the study. Mixed method research includes both qualitative and quantitative paradigms and thus the two are not mutually exclusive. The characteristics of the two methods appear in Table 1.

Table 1. Characteristics of Quantitative and Qualitative research

	Quantitative	Qualitative
The role of theory in research	Deductive	Inductive
Epistemological orientation	Positivist	Naturalist, Interpretive
Ontological orientation	Realist	Idealist, constructivist
Characteristics of research approaches	Objective	Subjective
	Impersonal	Personal
	Reductionist	Holistic
	Generalisation	Uniqueness
Types of data	Quantifiers	Describers
	Numbers	Words

7.2. Qualitative research method

7.2.1 *Thematic analysis of Braun and Clarke.*

The complexities and diverse approaches to qualitative research resulted in the different methods and analysis. Carter and Little identify the following methodologies: grounded theory approaches, narrative, life history, testimonial, and biographical, various ethnographies, participatory action research, phenomenographic traditions and case study approach.⁽⁵⁾ Braun and Clarke add conversation analysis, interpretative phenomenological analysis, grounded theory, discourse analysis and narrative analysis.⁽⁶⁾

These methodologies are based on epistemological (theoretical) position on which the method is based.⁽⁷⁾ Braun and Clarke introduce thematic analysis as a research method. It applies across epistemological approaches.⁽⁷⁾ The method provides a flexible research tool and can provide an in-depth and detailed reflection of data. Thematic analysis was initially described as a tool of identification of “thematising meanings”, but due to its generic application across all analytic methods, it evolved into a fully recognized method rather than a tool.⁽⁸⁾ The application of thematic analysis concerning health-related research is documented by studies including a wide-ranging group of subjects and scholarly areas including health conditions, for example, Hunting’s disease, multiple sclerosis and societal issues such as homosexuality.^(7,9) The thematic analysis describes data patterns across qualitative research. The method allows for the identification of specific themes to be explored during the research.

In an inductive approach, themes are identified out of the data set and may not be related to the researcher’s specific interest in the topic. The research is thus data driven rather than researcher driven. A researcher driven approach is theoretical thematic analysis during which themes identified are explored by predetermined questions as part of a semi-structured interview. The theoretic thematic analysis is driven by the researcher's interest in specific aspects of data. The data for analysis can be obtained by individual or group related semi-structured interviews. The Braun and Clarke method of thematic analysis of data is reflected in Table 2.⁽⁷⁾

Table 2. Method of thematic analysis⁽⁷⁾

Phase	Description of the process
Familiarising yourself with your data.	Transcribing data (if necessary), reading and re-reading the data, noting down initial ideas.
Generating initial codes.	Coding interesting features of the data in a systematic fashion across the entire data set, collating data relevant to each code.
Searching for themes.	Collating codes into potential themes, gathering all data relevant to each potential theme.
Reviewing themes.	Checking if the themes work in relation to the coded extracts (Level 1) and the entire data set (Level 2), generating a thematic ‘map’ of the analysis
Defining and naming themes.	Ongoing analysis to refine the specifics of each theme, and the overall story the analysis tells, generating clear definitions and names for each theme.
Producing the report.	This represents the final opportunity for analysis. A selection of vivid, compelling extract examples, the final analysis of selected extracts, relating back of the analysis to the research question and literature, producing a scholarly report of the analysis.

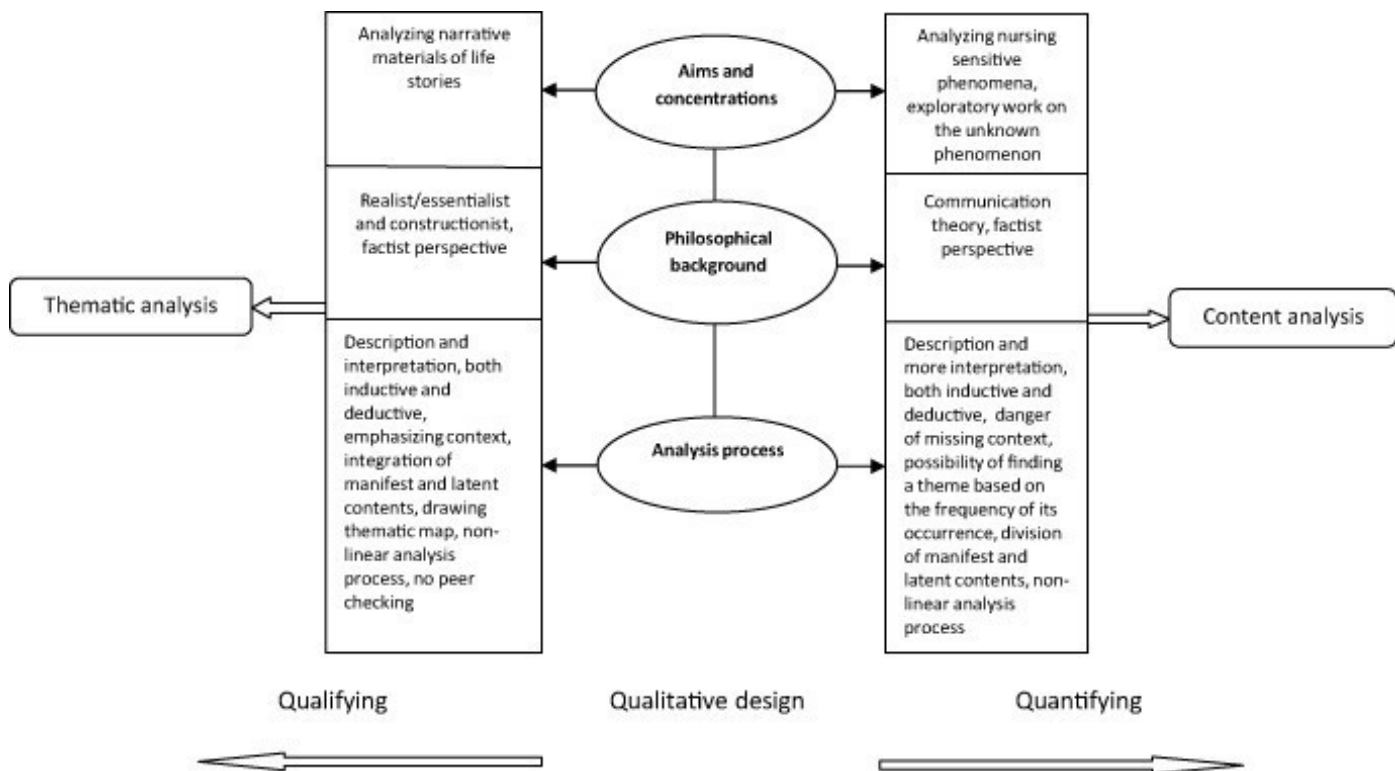
For health researchers concerned with understanding the experience of living with a particular diagnosis; patients’ or health providers’ perspectives on a particular healthcare intervention;

the ways in which new reproductive technologies re-configure women's experiences of pregnancy and childbirth or infertility, qualitative methods may be useful. These include the various methods used in qualitative research. To give one brief example: whilst quantitative research is useful when, for instance, comparing outcomes for mothers who delivered babies 'naturally' with those undergoing caesarean sections, qualitative approaches enable exploration of women's experiences of 'natural' and caesarean births (interpretative phenomenological analysis and grounded theory) and the meanings around 'natural' and caesarean births (discourse analysis). Similarly, they enable analysis of various stakeholders' perspectives (e.g., mothers, midwives and obstetricians) on decisions about managing birth (interpretative phenomenological analysis, grounded theory and discourse analysis) and how one perspective may become privileged over others in that process (discursive psychology and discourse analysis). ⁽¹⁰⁾

7.2.2 *Thematic analysis and content analysis*

Qualitative research methodologies are not a single research approach but encompass different theoretical (epistemological) perspectives that result in a range of approaches. Vaismoradi prefers the term "approach" to "methods" as it includes the associated theoretical viewpoint about the nature of the enquiry. ⁽¹¹⁾ Research findings generated by the enquiry can be placed on a continuum degree of transformation from purely descriptive to interpretation. ⁽¹²⁾ The main characteristics of the continuum of thematic analysis and content analysis are depicted in Diagram 1 and Table 3.

The different processes followed in data analysis appears in the Table 3. The two approaches, although different, can be combined as described by Green and Thorogood with thematic content analysis.⁽¹³⁾ A study on the performance of South African private-public partnerships illustrates the use of thematic content analysis. The research involved participants in seven high profile private-public partnerships in South Africa that was involved in the Fifa Soccer World Cup. Six senior personnel were asked to complete a research questionnaire. The research used thematic content analysis to identify private-public partnerships hurdles and success levels as themes. The contents of these themes are further described, for instance, the private-public



partnerships hurdles theme identified political interference as the main barrier to project success.⁽¹⁴⁾

Table 3. Comparison of phases

Analysis phases and their descriptions

Thematic analysis	Content analysis
<i>Familiarising with data</i>	<i>Preparation</i>
Transcribing data, reading and rereading the data, noting down initial ideas.	Being immersed in the data and obtaining the sense of the whole, selecting the unit of analysis, deciding on the analysis of manifest content or latent content.
<i>Generating initial codes</i>	<i>Organising</i>
Coding interesting features of the data systematically across the entire dataset, collating data relevant to each code.	Open coding and creating categories, grouping codes under higher order headings, formulating a general description of the research topic through generating categories and subcategories as abstracting.
<i>Searching for themes</i>	
Collating codes into potential themes, gathering all data relevant to each potential theme.	

Reviewing themes

Checking if the themes work in relation to the coded extracts and the entire data set, generating a thematic map.

Defining and naming themes

Ongoing analysis for refining the specifics of each theme and the overall story that the analysis tells, generating clear definitions and names for each theme.

Producing the report

The final opportunity for analysis. Selection of vivid, compelling extract examples, the final analysis of selected extracts, relating back to the analysis to the research question and literature, producing a report of the analysis.

Reporting

Reporting the analysing process and the results through models, conceptual systems, conceptual map or categories, and a storyline.

7.2.3 Scientific rigor in quantitative research.

The underlying philosophy of most quantitative research is that there is no one single truth or reality and that the research results depends on the researcher's perceptions and interpretations of them. The interpretation is thus subjective and relative. The endpoint is thus the result of the interaction between researcher and the researched under a particular set of conditions or

context.⁽¹⁵⁾ The close relationship of the researcher to the research topic results in questions with regards to objectivity. In view of the lack of objectivity proponents of quantitative research has been extremely critical of its value. In this regard, Archie Cochrane, founder of the Cochrane databases, regarded quantitative research as unscientific.⁽¹⁶⁾

Concerns regarding the scientific rigor of quantitative research have been addressed by Lincoln and Guba (Table 4).⁽¹⁷⁾ They initially described four criteria, adding a fifth later, to establish a framework for rigor. Descriptions and definitions with reference to quantitative research criteria appear in the table.

Table 4. Lincoln and Guba's principles for evaluating trustworthiness in qualitative research.⁽¹⁷⁾

Qualitative research	Questions that underpin the principles of qualitative research	Quantitative research concepts
Credibility	How can we be confident of the "truth" of the findings?	Internal validity
Confirmability	How can we be certain that the findings have been determined by the subjects and context of the inquiry, rather than the biases, motivations, and perspectives of the investigator?	Objectivity

Dependability	Would the findings be repeated if the inquiry were replicated with the same (or similar) subjects in the same or similar context?	Reliability
Transferability	Can we apply these findings to other context or with other groups of people?	Generalisation
Authenticity	Have people been changed by the process? To what extent did the investigation prompt action?	

Rigor may be defined as “the quality of being extremely thorough and careful”. Cypress argues that reliability and validity are more appropriate to use in quantitative research than rigor. This represents an attempt to standardize criteria across qualitative and quantitative research. She, however, prefers the word rigor to trustworthy in naturalistic studies.⁽¹⁸⁾ In contrast to Cypress, Johnson reiterates the appropriateness of the Lincoln and Guba criteria.⁽¹⁹⁾ The controversy surrounding the scientific rigor of quantitative research results in researchers describing and discussing how scientific rigor is maintained during their research.

7.3 Qualitative studies and cervical cancer

Qualitative studies related to cervical cancer vary in study structure and methods of analysis. The majority of studies used semi-structured questions followed by a thematic analysis method. (Table 2). A grounded theory approach with the inductive identification of themes is the basis of Dreyer’s identification obstacles to successful cervical cancer screening in public sector primary healthcare clinics.⁽²⁰⁾ Zeng uses the same methodology to describe the experience of a

cervical cancer survivor. The grounded theory approach uses smaller numbers of participants with an in-depth analysis of data. In studies of larger participants, a structured interview with pre-tested questions is more appropriate as illustrated by Maree's study of 963 men and their knowledge of cervical cancer.⁽²¹⁾

7.4. Tertiary management of cervical cancer.

In South Africa, the majority of women present with an advance stage disease require radiation or chemoradiation therapy.⁽²²⁾ Table 4(Page 173) reflects qualitative studies of women with invasive cervical cancer. South African women presenting symptoms of cervical cancer instinctively knew that something was wrong with them, but lacked the knowledge or awareness of what was required to prevent pre-cancerous lesions from developing into advanced cervical cancer. The women's initial contact with the health care system, whether by a registered professional nurse, medical practitioner or traditional healer, did not result in correct management. The women repeatedly sought health care before they were eventually managed. The group were divided in terms of their belief in traditional healers. Most of the women consulted a traditional healer only after the health care system had failed them. The role of support structures, including a family member, more importantly mothers and daughters and then eldest sons, or a boyfriend, doctor, employer, woman friend or neighbour, was important.⁽²³⁾ The lack of knowledge and failed communication of the correct symptoms with a resultant delay in diagnosis is highlighted in a further South African study by the following comment:⁽²⁴⁾

“I went to the clinic every month for my blood pressure medication; I was too ashamed to tell the nurses about the vaginal bleedings and offensive vaginal discharges I had experienced. I only complained of a headache and fatigue.”

A study of the role of life partner support among women receiving treatment for cervical cancer describes a lack of knowledge of these women of what was happening to them. Their life partners also lacked knowledge. In African culture, men considered regular sex to be essential for their healthy functioning. The women feared resentment and rejection due to the disease-

related inability of them to have sexual intercourse. Some women received tangible and financial support from their life partners.⁽²⁵⁾ Zambian women receiving treatment for cervical cancer lacked the knowledge to deal with their disease and suffering. Some felt desolate and considered suicide:

“I would enclose myself in the house because a lot of people were telling me that I am smelling like a poisoned rotten rat which has died. Because of this talking, I almost killed myself. I wanted to drink rat poison. I sent my children to go and buy rat poison.”

Chinese cervical cancer survivors identified the impact of cervical cancer on their physical, psychological sequelae, family distress, financial burden, and disruptions to their social functioning and sexual life as significant. Chinese survivors of cervical cancer identified their sexual life as one of the essential indicators of quality of life. Nevertheless, there were positive gains that were reported by these survivors, including changes in their outlook on life, treasuring their life, and better family relationships as reflected by the following comment:⁽²⁶⁾

“We have no need to complain too much about life, as we will all die someday. This is a natural law. Getting cancer . . . is fate and we have to face our own fate and other kinds of suffering in our lives.”

In South African women, late effects of radiation therapy resulted in decreased sexual function, pain, and fatigue. They were positive about their future owing to their faith as a woman stated:⁽²⁷⁾

“I believe in God, to move on yes. If you believe in God, nothing can happen to you. Cancer, it’s not the end of the world. The time will come when everybody is going to die.”

7.5 Conclusion

The qualitative studies of cervical cancer, its etiology, prevention, and treatment identify aspects that should be addressed in the further management of the disease. There are several indications that a lack of knowledge exists. This includes healthy women who have to alter their lifestyle and make decisions concerning prevention and early diagnosis by cervical

cytology. The lack of knowledge includes health care providers who need to implement preventative programmes. The culmination of lack of knowledge on the women and health care providers results in ineffective programmes. Women with abnormal cervical cytology results requested more information reiterating the lack of knowledge. In women with cervical cancer, the qualitative studies identify a lack of knowledge that results in suffering. This suffering is increased by the lack of knowledge in the community with resulting stigmatisation. Poor knowledge of life partners further adds to the situation. The experience of cervical survivors reflects an acceptance of the sequelae of the disease and its treatment.

In summary, qualitative studies indicate a definite need for a better education and information at all levels of the population and providers. This will result in improved uptake of preventative measures and increase compliance in adherence to screening programmes. Improved information and communication to women with cervical cancer is needed. Qualitative research lends a voice to women to identify their priorities with regards to all aspects of cervical cancer. These include the primary prevention of the palliative care phases of the disease. The needs of women thus identified can serve as a departure point to plan the provision of health services inclusive of education on preventative measures vaccination, screening, and treatment. Qualitative research forms the basis for the development of quantitative research. Research themes, identified by qualitative research are incorporated into structured questionnaires that can be used in clinical practice as well as research. Quantitative and qualitative research are complementary modalities in enhancing women with cervical cancer's QOL and furthering research into improving their care.

Table 4 Studies on the qualitative analysis of women with invasive cervical cancer

Author	Country	Aim of study	Participants	Number	Method
Maree(21)	South Africa	Evaluate men's knowledge about cervical cancer.	Community recruited	963	A structured interview and a pre-tested questionnaire.
Van Schalkwyk(23)	South Africa	To understand the routes women followed by first signs and symptoms of the disease to receiving treatment.	Women diagnosed with cervical cancer and receiving radiotherapy.	15	Phenomenological analysis based on the semi- structured interview.
Issah(24)	South Africa	Describe the women's experience of cervical cancer- related signs during the initial consultation with healthcare professionals	Women treated for cervical cancer.	12	Semi-structured interviews.

Maree(28)	South Africa	To describe life partner support among women receiving treatment for cervical cancer.	Women receiving treatment for cervical cancer	17	Preset questions with thematic analysis.
Ntinga(27)	South Africa	Describe the late effects of cervical cancer.	Women diagnosed with cervical cancer referred for treatment	16	Grounded theory with thematic analysis
Maree(25)	South Africa	Describe underprivileged women's experiences with cervical cancer.	Women diagnosed with cervical cancer referred for treatment.	19	Open-ended unstructured interviews.
Zeng(26)	China	To explore the meaning of “Quality of life”.	Cervical cancer survivors	35	Grounded theory

Maree(29)	Zambia	To describe women's experiences of cervical cancer	Women receiving treatment for cervical cancer.	21	A phenomenological approach using semi-structured interviews.
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Chapter 8. The lived experience of women with cervical cancer in the private health sector of the Western Cape, South Africa: An exploratory, qualitative study highlighting the duality and dichotomy of psychological coping and defence strategies.

8 Introduction

Advanced cervical cancer remains a significant health burden in South Africa with an incidence of 26,4/100000.⁽¹⁾ Early stage disease is amenable to radical curative surgery. Radiation therapy and chemotherapy is used in advanced stage cancer. Most South African women present with advanced stage disease. Treatment offers limited survival with a 35% five-year survival for stage III.⁽²⁾ In these circumstance, the assessment of the QOL is important for future decisions on treatment regimens to be used. Objective, quantitative evaluation of cervical cancer cases' experience of the disease and its treatment by structured questionnaires to assess the QOL allow for statistical analysis in clinical decision making. Examples of these questionnaires are European Organisation for Research and Treatment of Cancer (EORTC) QLQ C30 and CX24 (3,4,4). The domains assessed in the QOL questionnaires are the result of the inputs by various medical disciplines. After consensus, the final questionnaire is constructed and validated. The questionnaire allows for quantitative analysis of the patients' subjective experience (QOL) of their disease and treatment. The predetermined set of questions, as identified by the medical fraternity, does not allow the patient to identify her set of priorities in determining her experience of cervical cancer.

Qualitative research enables the patient to identify factors relevant to her experience of cervical cancer. The emphasis shifts from a provider identified list of priorities to a patient centred process. Qualitative research reports of women's experience in resource rich countries focus on preventative interventions for cervical cancer.⁽⁵⁾ The application of this research to resource constrained countries should be moderated by local cultural, political and historic factors. In the South African context, the implication of historical disempowerment, political instability and health care discrepancies are relevant.⁽⁶⁾ Previous qualitative studies of South African women with cervical cancer focus on screening ,men's knowledge of the condition and

partnership relations before the diagnosis.⁽⁷⁻⁹⁾ Expression of signs and symptoms during treatment and treatment related effects were the focus of other studies on women during treatment.⁽¹⁰⁾ The aforementioned studies were done in Tshwane in Gauteng Province. The majority of participants were Black with a low literacy rate. The lived experience of women with cervical cancer is influenced by ethnicity and therefore findings of the aforementioned studies would not necessarily reflect experiences of other South African regional and ethnic groups.⁽⁶⁾

Qualitative data serve as important indicator of a specific study group's experience. The descriptive data serves as departure point for further analysis to identify psychological therapeutic intervention to support women with cervical cancer. The context of the current study is women with cervical cancer managed in the private health sector in the Western Cape. Below mentioned are the current study aims:

- 1) To describe the lived experience of women during diagnosis, treatment and follow-up of cervical cancer in the private health sector in the Western Province, South Africa.
- 2) To interpret these reported experiences using the Kübler-Ross model of bereavement as reference basis.
- 3) To analyse these responses to identify defence mechanisms and coping strategies used by the women to manage their situation.
- 4) By drawing upon these responses construct an argument on the synchronously dualist and dichotomous nature of psychological defence and coping mechanisms.

8.1 Psychological response to stress

8.1.1 Kübler-Ross model

Elizabeth Kübler-Ross described the model of bereavement as a series of emotional experiences of terminally ill patients prior to death. The five stages are: denial, anger, bargaining, depression and acceptance. Kübler-Ross used qualitative research methods, albeit the fact that is not official named as such in her book, to study the lived experiences of terminally ill patients to construct her model. She later expanded the use the model to include, amongst other, any form of personal loss including divorce, incarceration and onset of disease.⁽¹¹⁾ Other models of bereavement exist and the Kübler-Ross model, although been criticized, has widespread acceptance and usage. Criticism of the model include the initial hierarchical and linear unidirectional steps towards grief. Further concerns raised were imprecise definitions, failure to present a dynamic process, lack of empirical evidence and lack of validation across cultures and historical periods. The limited focus on interpersonal processes was also raised as critique. In adapting the model to a multi-directional, non- hierarchical model it becomes a well-recognized tool.^(12,13)

8.1.2 Reaction to stress

In describing the reaction to stressful life events two theoretical perspectives may be used.

These are the Lazarus cognitive stress theory and Horowitz's stress response syndrome.^(14,15)

Lazarus defines psychological stress as a "*particular relationship between the person and environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her wellbeing*". Accordingly, the primary appraisal by the person identifies the particular event as a threat that may be harmful. The secondary appraisal assesses if sufficient resources are available to deal with the threat. Stress follows if the resources is deemed insufficient. The stress response is twofold. The first response is problem-focussed and attempts to deal with the threat by changing or managing it the second stress response attempts

to address and cope with the emotional reaction to the threat. A further dimension to coping is the confrontation-avoidance emotional response.⁽¹⁶⁾ This process involves confronting the stress and try to adapt to it. Alternatively is to temporarily to avoid dealing with it. The interplay between these processes are non-sequential and oscillation between these occur to cope with the stress

The Horowitz stress response syndrome describes the normal manifestation to a traumatic personal experience. The syndrome is characterized by the opposing reactions. Intrusion results in compulsive re-experience(“flashbacks”) of feelings and ideas related to the event. This results in nightmares, sleep disturbance and hypervigilance. In contrast avoidance is a denial reaction resulting in amnesia and denial. The difference between normal and abnormal reaction to the traumatic personal events is defined by the intensity and frequency of the reaction. Post-traumatic stress disorder is an example of the diagnostic application of the Horowitz syndrome.⁽¹⁷⁾

or her wellbeing

8.1.3. Defence mechanisms

Adaptation, resilience, coping and defence mechanism are used as interchangeable in reported studies. Clear difference exist that require further discussion. The differences translate into possible emotional and psychological support to patients experiencing threat or stressors. Defence mechanisms and coping strategies are both directed at the same threat but involve different cognitive processes.

8.1.3.1 History of defence mechanisms in psychology

Sigmund Freud describes the concept of defence mechanism as a mental operation that kept painful thoughts and affect out of conscious. Anna Freud confirmed and expanded the concept as protective by “warding off “anxiety and guilt feelings this regard two processes repression and projection play a central role.⁽¹⁸⁾ Repression is the process of suppressing a thought or

desire until it become unconscious. Suppression is the protective process of humans to defend themselves against conscious impulses or qualities by denying their existence in themselves by attributing them to others.

In criticism to the psychoanalytic process Holmes concluded that the majority of memory results previously attributed to repression were better explained by differences in attentional processes. Attentional processes are modified by individual circumstances e.g. cultural or societal unacceptability of specific words resulting in non-verbalisation. According to Holmes projection is best explained by an attribution paradigm resulting in blame-shifting between self and others.⁽¹⁹⁾ Subsequently to the work of Holmes defence mechanisms fell in in esteem in psychology community.

Contemporary psychology broadened defence mechanisms to include the maintenance of self-esteem and protection of self-organisation. These changes were accompanied by more reproducible measurement of defence mechanisms. Valliant suggested different defence mechanisms arranged in hierarchical order Vaillant categorize and describe defence mechanisms into four hierarchical levels of mature, narcissistic, immature and neurotic defences. These mechanisms with examples appear in table 1(20). An alternative, expanded defence Functional Scale, was introduced in the DSM IV. Due to continued controversy, it was omitted in the subsequent DSM VI.

Defence mechanism	Examples
Mature	Altruism, Anticipation, Asceticism, Humour, Sublimation
	Suppression
Narcissistic	Denial, Distortion, Projection

Immature

Acting out, Blocking, Hypochondriasis, Introjection

Passive-aggressive, Regression, Schizoid fantasy,
Somatization

Neurotic

Controlling, Externalization, Inhibition, Intellectualization

Isolation, Rationalization, Dissociation, Reaction formation

Repression, Sexualisation

Defence mechanisms are surrounded by controversy due to lack of terminology and definitions. Defence mechanisms were previously included in the Diagnostic and Statistical Manual of Mental Disorders (DSM) but have been omitted in the latest DSM 5 edition.⁽²¹⁾ Part of the negative approach to defence mechanisms are their origins in the Freudian psychoanalytic movement. Freudian and Neo-Freudian arguments popularized defence as a set of psychological mechanisms by which individuals distort reality to manage distressing feelings, particularly anxiety. Consolidating her father's work Anna Freud introduced several defence mechanisms. She advanced the notion that individuals have preferred ways or styles of reacting to stress and linked certain defensive styles to psychopathology.⁽²²⁾ Defence mechanisms are thus construed as psychopathological rather than a normal non-pathological response. Further criticisms on defence mechanisms are their reliability and validity due to the difference in the interpretation by the person in the stressed situation and the interpretation by analysts. Despite these reservations defence mechanisms are best summarized by Valliant:⁽²³⁾

"Nevertheless, if the study of defences is problematic, their greatest value is validity. Thus, as often as Freud's discovery of adaptive self-deceptions is dismissed as unreliable, defences are rediscovered because they do exist. Defences are as ephemeral and as real as rainbows-a trivial but easily grasped example. Defences are as ephemeral and real as the Heisenberg Uncertainty Principle in physics-an absolute critical but less easily discussed. Examples of

Rainbows, the Uncertainty Principle, and defences are all relevant to our realistic conceptualization of nature. Yet, because they all represent dynamic process and not substance, all three will always be elusive.”

8.1.3.2 Defence mechanisms and coping strategies

According to Cramer adaptation to stress occurs by coping and/or defence mechanisms. Overlapping points are present between coping and defence mechanisms but they may be separate on theoretical points and in therapeutic approaches. Defence mechanisms and coping strategies are both directed at the same threat but involve different cognitive processes. Cramer describes the differences between the two mechanisms (Table 1.)⁽²⁴⁾

Table 2 Differences in coping and defence mechanisms

Coping process	Defence mechanism	Difference
Conscious	Unconscious	Critical
Used intentionally	Nonintentional	Critical
Situational determined	Dispositional	Not a critical difference; a matter of emphasis
Non-hierarchical	Hierarchical	Not a critical difference; a matter of emphasis
Associated with normality	Associated with pathology	No difference, when self-report and context are controlled

Cramer’s definition was supported by Miceli et al and further elaborated by adding a further criterion. Miceli et al add that defence mechanisms may be manipulative versus coping

strategies representing a revision of an individual's mental attitude to threat(25). Manipulation becomes an unconscious alteration of mental attitude triggered by the goal to avoid negative affect. In contrast revision entails a conscious change in mental attitude to repel and reject threat. Manipulation of content and magnitude of a threat results in reduction and possible elimination of the threat. Revision entails recognition of the threat's content and magnitude but revise the reaction to it as a meta-goal. That is, looking beyond the immediate threat, and focussing on further afield than immediate consequences and results. Defence mechanisms (manipulation) thus minimize the reality of the threat and thus avoid suffering. Coping strategies (revision) recognize the magnitude and content of the threat and deal with it by contextualizing the immediate situation to a long-term goal(25).

8.2 Methods

8.2.1 Research design.

This study is an exploratory, qualitative study. A qualitative approach is chosen as the most appropriate methodology to explore the experiences of women with cervical cancer because it allows to make an in-depth inquiry and to incorporate complex and rich insights from the women's personal experiences. Bless et al. explain that exploratory research is appropriate when there is little knowledge available regarding a particular research topic or question and new insights into phenomena are needed.⁽²⁶⁾

8.3.2 Data collection

Women who have been diagnosed and completed treatment for cervical cancer at private radiation and gynaecology oncology practises in the Western Cape Province was invited on an individual basis to participate. Before the interviews started, informed consent from each participant was obtained. In addition to the informed consent, a short biographical questionnaire was completed by the participants.

8.3.3 *Ethical aspects*

The interviews were conducted by the co-investigator; Dr. Pretorius, a counselling psychologist, who was not personally involved with the clinical management of the patients. This was to make sure that the participants could freely express themselves about their experiences and to prevent them from giving answers that they think their doctor would want to hear. The invited participants were informed about the relevance and nature of the research. They were reminded that their participation was entirely voluntary as well as that they had the right to withdraw from the proposed study during any stage without experiencing any negative consequences. The participants were informed that they would incur no additional expenses if they wished to participate in the study. Informed consent, which included their permission to record the interview, was first required from the participants before the interviews started. Each participant was assigned a number when the data was analysed in order to protect the participants' anonymity. It was anticipated that the interviews would take between 60 and 90 minutes to conduct. All of the interviews were tape-recorded, with the participants' permission, to transcribe them verbatim to perform the necessary analyses. Transcribing of the voice recordings were done by professional transcription services. The researchers used both recordings and transcriptions to serve as quality check. Coding was jointly done by both researchers. Once the tape-recorded interviews were transcribed, they were kept safe and secure in a locked drawer in Dr. Pretorius's office. The only anticipated risk was that the participants may experience emotional discomfort and/or distress during the interview due to the personal nature of the interview. If this was to be the case Dr. Pretorius, who is a Counselling Psychologist would attend to the situation and if required she would then have referred them to appropriate health care professionals.

After consent, a semi-structured interview followed, which consisted of broad, open-ended questions about the women's experiences. Themes were explored as reflected by attached items

(Table 2). All the interviews were tape-recorded, transcribed followed by the analyses. The local Ethics Committee approved the research protocol N13/02/020.

Table 2 Interview questions

1. Tell me about the process of getting to a diagnosis of cervical cancer.
2. Tell me about your experience of living with cervical cancer.
3. What are some of the challenges that you face? Or What makes it difficult for you to cope with cervical cancer?
4. What are the factors and/resources that make it easier for you to cope with cervical cancer?
5. Tell me about the financial impact of cervical cancer on your life.
6. Tell me about the impact (positive and negative) of cervical cancer on your personal relationships specifically with regard to
 - a. Your husband/partner
 - b. Your children
 - c. Extended family
 - d. Friends
 - e. Broader community (e.g. church)
7. It is common that women with cervical cancer experience sexual problems. Tell me about your experience.
8. Do you want to share anything else that you feel is important for me to know?

8.3.4 Analysis

The thematic analysis method of Braun and Clarke was used.⁽²⁷⁾ In the first step of the analysis, the researchers familiarised themselves with the data through the transcription process by listening to the interviews as well as reading through the data several times, while thinking about the possible themes. After that, initial codes for the transcribed information were

generated, which involved the manual coding of relevant features of the entire dataset. This step was necessary to organise the data into meaningful groups. In the second step, themes were identified by arranging possible codes into themes. After that, the themes in the document were defined and named to refine each theme. Identification and naming of themes can be done to various approaches as described by Braun and Clarke. The current study used a deductive, semantic approach with themes name in objective fashion. The choice is based on previous report qualitative studies in health-related topics. Finally, a report was produced with all the major and subthemes. The report is substantiated with compelling, vivid extract examples from the transcripts. Direct quotations from the interviews with the participants are used to illustrate themes and categories. ⁽²⁷⁾

Approach	Explanation
Inductive	Coding and theme development are directed by the content of the data.
Deductive	Coding and theme development are directed by existing concepts or ideas.
Semantic	Coding and theme development reflect the explicit content of the data.
Latent	Focuses on reporting an assumed reality evident in the data.
Constructionist	Focuses on looking at how a certain reality is created by the data.

8.3 Results

The biographic data of the 11 women reveal a mean age of 53(range 42-81) years and a mean time since diagnosis of 6 years 8 months (range 3 months -18 years) (Table 3). The themes identified cover a range of aspects.

Participant	Age	Marital status	Home language	Ethnicity	Time since diagnosis
1	55	Married	Afrikaans	White	1 year 9 months
2	47	Married	Afrikaans	White	3 years
3	81	Married	Afrikaans	White	3 months
4	68	Widow	Afrikaans	White	8 months
5	42	Divorced	Afrikaans	Coloured	3 years 6 Months
6	55	Married	English	White	5 years
7	47	Single	English	White	6 months
8	52	Married	Afrikaans	White	11 years
9	49	Single	English	White	15 years
10	40	Married	Afrikaans	White	15 years
11	49	Married	Afrikaans	White	18 years

Table 3. Demographics of study participants

8.3.1 Themes

8.3.1.1 Medical aspects

Consultations.

This overarching theme includes the initial consultation with medical professionals, the patient's personal opinions, the diagnostic and treatment events as well as the subsequent follow-up visits. The initial diagnosis was met with disillusion and women reflected on their health aspects to illustrate a feeling of disbelief.

I never had any trouble previously. Had two normal pregnancies followed by a normal birth. It makes one think and realize that it could happen to anybody even if your life as healthy as possible. Participant 1.

I have been healthy and happy so far. At 11 years of age, I had surgery for a burst appendix and a further surgery at 12 years of age. Those were the only times I was hospitalised. Participant 2.

Diagnostic process

A sense of denial is expressed due to the shock associated with the grave diagnosis. The failure of the annual cytology smears, despite the patient's diligence, adds to the disappointment with the medical system.

And yes, I regularly went for annual gynaecological visits. I attended the gynaecologist in February and after the Easter weekend, the gynaecologist phoned and asked me to come for a consultation. Something came back from the laboratory that was not a 100% well. I really got a fright because it was for the first time that something was wrong. He said it is not

urgent but wanted to check out the situation under general anaesthetic. Yes, I went on the Tuesday for the procedure and on Friday received a phone call that there were serious problems and that he had made an appointment to see a gynaecologist who specialises in cancer cases. I went and got the news. A person is quite upset. So, unpredictable.

The initial disbelief and shock that the patient expresses are followed by uncertainty but relief at the speed of the management.

Well maybe because it happened so quickly I did not have time to digest and handle the situation. I think it is a shock for anybody when it happens to them. Participant 1

An attempt is made to rationalise the situation by referring to the experience of friends.

Yes, I still cannot believe I had cancer. I never had bladder problems and never had an infection in my female parts. I still have everything that should be there. I never had a bladder infection like several of my friends had. You know the feeling of wet panties. There never was such a thing. So, you can understand how shocked I was to hear that I have cancer. I could not believe. I told the doctors this and just looked at them. I could not believe that there was something wrong with me. Participant 3.

Routine gynaecological consultations

A sense of self-recrimination is expressed due to the absence of regular gynaecological screening

No, I never had pain and I must honestly admit I never went for my Pap smears regularly am not going to return to that but I know I did not go so it could not be detected in an early stage. So yes, I feel partially guilty. Participant 2

I didn't go to the gynaecologist once. And I mean I know, I mean I'm supposed to go once a year for your check-up blah, blah, blah. I didn't go, because it's one of those things where

you know that you need to go, but you never find the time, because there isn't a problem. You only go to the doctor when there's a problem.

Women expressed their guilt on not attending a regular screening visit or to returning to gynaecologist after persistent symptoms of bleeding. These admissions form part of an initial process of coming to terms with a perceived self-inflicted situation.

So anyway, so I just left it and left it and then a year ago, I got a message duh, duh, duh your loop, it's time for it and I thought yes, yes, yes, okay I'll get there, I'll get there, I'll get there kind of thing, and then probably last year, yes last year it started. But of course, I left it and I left it and I left it, and it got to a point, because I was still with my fiancée then at the time, it got to a point where I wouldn't bleed constantly, but I'd be fine, and I wouldn't be bleeding, but then obviously when we had sex, it would get out of hand. And he kept on saying to me, you've got have this thing out, and I said yes, no, no, and it was a big issue, but anyway. So then eventually, because then we weren't together anymore, so that was, you know what I mean. But I still knew I had to go because obviously...Participant 7

Surgery and test results

Surgical treatment resulted in loss of reproductive function and this added to the dismay of the woman.

So, it was a total shock to me. I had no idea that there could be something wrong with me. So, it just happened. It was terrible for me because I still wanted to have a child. Participant 8

Service delivery/Transport

The logistics of traveling between facilities resulted in distress. A degree of self-blame is expressed as the traveling is due to the patients weight restricting treatment to a particular radiation facility. Gratitude is expressed to her son and ex-fiancé.

Because then what they did, was they obviously diagnosed and they said was that I had to have six weeks' treatment, everyday radiation for five days and one-day chemo for the six weeks. And that was fine because I could have chemo here at Hospital A, but then I had to go to Hospital B for my radiation, because the bed has a limit, a weight limit. So, at first, I, well okay, it's my own fault for being overweight, but I think to myself now I've got to get into my little old car, and I've got to travel all the way to Hospital B every single day for six weeks. That that was more stressful to me than anything else. But luckily, my ex-fiancé took me once or twice a week when he could when he went that way. My son helped me once or twice.

Participant 7

Side-effects

Despite information on radiation treatment-related side effects were given to the patient expressed a need for better support. An information leaflet and a counsellor were inadequate to prepare the patient for the treatment and its side-effects.

No. I mean the chemo really wasn't that bad. The radiation, I don't think they prepare you enough for it. I mean they should literally say to you it is going to be bad, literally. Well I know they don't want to do that, but there must be a way that they can prepare you better for it. I mean they give you, I've still got it, they give you a little leaflet and they tell you this and that, but that, it's very broad and it's also not specific to you. It's for cancer in general.

There is a counsellor that can help you, but I mean I still thought to myself, well you know, because they make it sound like the counsellors are more for if you're got blocks of cancer because, for the family, you know what I mean. You know to prepare that it might be bad.

You know what I mean? Participant 7

Follow up consultations

Upon completion of the treatment, follow-up visits are required to monitor the diseases' status and potential treatment-related effects. Completion of therapy brought relief but started a new cycle of uncertainty due to possible disease recurrence. Despite assurance, a sense of worry persists.

I had to come for a follow up every three months. Two weeks before every follow-up visit, I went extremely nervous. You always hope that everything would be fine. It stressed me a lot. After the visit, I stressed again while waiting for the test results. Then, I heard the good news that everything is fine and that my follow up visits have been changed to six months. Less frequent follow up is welcome but I still worry that the disease will return. There will always be that uncertainty. Participant 1

Then the anti-climax of completion of treatment. The scariest is the three month follow up visits with scans. You must prepare yourself for the results of the examination and the scans. I think that is the worse part of cancer. To hear whether you are fine or not. It is like a roller coaster. The one moment you feel fine but then the scans again cause stress. This first time I was in remission and I thought I was fine and then cancer came back. So, I thought I will need to live with this uncertainty. Participant 2

You've always got this sword hanging over your head all the time. So, I think in the beginning, it's quite daunting. I mean it's just the waves of negativity that you have. So obviously, each year, as you go, and you've got your six months, three monthly, six monthly, and yearly. So, as you sort of getting to those various milestones, it is as if a sort of the sword is hanging further away, let's put it that way.

Look, there's always that bit of stress when you go for your checkup, and even on a day to day basis when you feel something. Oh, you know, you're not feeling well or whatever, that's the first thing that comes to your mind. Participant 6

But other than that, I think you just carry on normally as if things are okay. I suppose I'm a little bit anxious for my check-up at my gynaecologist obviously, and if that's clear, then I think I will feel a lot better. Because you must wait so long now. So, I think that's the thing. And I think if they could tell you straight away that would be nice [laughs]. If you could just go for a check-up and they say no, everything's great. Participant 7

8.4.1.2. Family history

Patients referred to the presence or absence of a family history of cancer. Cervical cancer has no genetic predisposition and the women's comments reflect on the lack of information they had.

And, we don't really have, or we don't have cancer in the family. I've never actually in my inner ring been touched by cancer. Obviously, I had read about it and heard about it, but in my immediate circle, I had never ever heard about anybody with cancer, so it was me, which I think, in my case, was a very good thing. Participant 6

I come from a healthy family that was never sick. We have never been hospitalised. This was my first time in a hospital for an operation. It was a huge shock initially.. Participant 10

I come from a family with a lot of cancer cases. From my mother's and father's side. These were different types of cancer including bone marrow cancer, bone cancer, and stomach cancer. So, I have always been vigilant. Participant 1

8.4.1.3. Increased awareness/caution

By referring to friends and prominent people with cancer, women interpret their disease in a wider context. This allows her to feel part of a "bigger" group and diminishes feelings of isolation.

Look, there's always that bit of stress when you go for your checkup, and even on a day to day basis when you feel something, oh, you know, you're not feeling well or whatever, that's the first thing that comes into your mind. And suddenly everybody, just about every second

person you know now has got cancer. So... It's quite daunting. Yes, then you become far more aware and you start doing research about cancer and radiation and chemo, what are you getting yourself in for? What is this? What is that? Then you sort of open this whole new world in your life that you were, I won't say oblivious of, but you know, like I kind of read Lance Armstrong's book about where he sort of conquered testicular cancer and all that kind of thing, but it was like there is no immediacy to it. And suddenly you start realizing oh but you find this person's son was diagnosed with cancer, and this one and that one and that one. And suddenly you're just living in a cancer world kind of thing. Participant 6

8.3.1.4. Sexual impact

Sexuality and reproductive ability are central in this references as cervical cancer is a disease of reproductive organs and its treatment can result in decreased sexual function due to vaginal stenosis. A change in body image occurs due to surgery with resultant fear of a partner's rejection. Ambivalence is expressed towards future relationships

Well, I mean there's no sex, let's put it that way for a long time. So, obviously, and your husband is still a sexual being, so you need to plan, you know what I mean? So, that is, I mean it's difficult for them. More so for us as women, because we very easily turn off our sex drives, but for men it's different. So, you know you must try and be more considerate of your partner's needs as well. So, fortunately, we do have a very good relationship sexually, so I was managing to satisfy him, I could sort of, but it's still, even at this stage, quite a difficult...Participant 6

You're obviously a little bit aware of scars and that maybe your body doesn't work in the same way, and obviously, we only know that when we go into a relationship. But when I did meet someone briefly, and then I did meet someone and then it was a much easier process than I thought it was going to be. But it was quite a hump to get through. I mean again, I didn't marry him, but I don't know, I often wonder if in the back of my mind I may be more

cautious about marrying someone obviously way past child-bearing age now, but I don't know. I often wonder if that were something that maybe was an excuse for me not to meet anyone, or literally if there just isn't anyone out there. Participant 9.

8.3.1.5. Religion

Religion forms a part of the support system by the individuals own spirituality and those around use religion as a support structure.

Even for me as a Christian, the events were a roller-coaster. I am a very spiritual person and because I am of an older view, things seem different to younger people. I have the certainty of my Christian ship and does not view cancer to have affected me because of my wrongdoing. I have spoken to people who view cancer as a punishment for what they did wrong. I do not hold the same opinion. I believe that my strong belief system served me well. Religion definitively makes a significant difference. Participant 2

God was very very good to me. I prayed " God, please prove them wrong " I prepared myself daily for treatment and did what they suggested. Yes, it is the power from above that I could carry on with treatment and my daily work as a baker. I feel this provided me with certainty and served as my support. That is what I clung to. Participant 3

Look, I did not become angry or felt sad upon hearing the cancer diagnosis. I just said to myself "It is cancer". It can be beaten. It is in God's hands. I asked God to provide me with the strength. I am not a converted person but live close to God. I feel converted in my own way. People prayed for me. I believed that God's will be done. God knew I had an elderly mother and children at home who needed my care. I prayed that He would make me the strong one and He did. Participant 5

Okay, I'm not a specifically religious person, my husband is a Greek Orthodox, so he is. I wouldn't say he's a staunch Orthodox, but he goes to church occasionally and stuff like that, so... So, I wouldn't say religion specifically played such a huge role. Participant 6

My one friend, the one that's overseas, is very religious, so it's very difficult for me because I'm not. So, she was like "Oh, I'll pray for you". You know, that's her thing and that's fine and we have an understanding about that, but I don't, no, not at all. Participant 7

8.3.1.6. Social support

Support from close relatives, for instance husband and family and more extended friends form an important support network. Friends and family serve as a support system but the family's wellbeing has an impact on the patient's own stress levels.

Well, I think your family support system is very important, you know, and I had fabulous friends as well who came and helped me and supported me. And I mean my husband was amazing.

Participant 6

My husband, family, and everybody supported me and helped a lot to get through the whole process. I am certain that I would not have been able to manage without all the support from my husband, family, and friends.

Participant 10

I have a fantastic support system of immediate and extended family, friends. Participant 1

I need to go for chemotherapy after this interview. My family is going on a weekend to a resort. They feel ashamed that they will be enjoying themselves while I am sick. Fortunately, they saw that cancer did not cause me to lose weight or appear ill. My friends also commented that I did not look like someone with cancer.

Participant 2

No, no. I'm a bit of a stubborn old goat, really. Because I didn't even tell my family.

Yes, obviously, my son knew because he was with me. My ex-fiancé knew because he was around. Well now around, we were still, we're still friends, and he helped me with, I had to move in between the process as well, so he helped me move. My sister, who is overseas, and my friend who is overseas and my boss helped me. That was about it. That's all, but my dad's very ill, so I didn't want my family to know and, it was a whole big story, but whatever. But yes, so I think, I suppose I should have, maybe I should have gone and spoken to somebody and I would have felt a little bit better about the whole thing. But I just felt like I was bothering them.

Yes, it was. You know at sometimes I thought ah, it would be so nice if somebody could just make me a cup of tea or something. But yes, I managed and it was alright.

*Participant 7***8.3.1.7 Information**

Information was obtained by the women themselves by reading or by being supplied a general fractionate by the internet, which served as a further information source. Information serves as a support. The lack thereof, on the other hand, leads to further discomfort and suffering.

I think reading literature. I mean, reading about other people coping with this, with the various things, I think that's important. I think to be able to know that you're not the only person going through that, and to find out how did other people cope, so that you have these sorts of little avenues that you can maybe explore yourself of how to, you know, how do you wash? What do you do, you know those little tips and hints and stuff like that? Yes, that was helpful. Yes, even my GP, I must say my GP was fantastic. Yeah, I think there's not enough

literature for women with cervical cancer, in the sense of when you go and be diagnosed, to have a nice little book or booklet to say okay, this is where you are, this is what's going to happen to you, this is how you can cope with it. Yes, so it is. The internet was helpful, yes. But it would have been...Participant 6

8.3.1.8 Coping

The ability to cope is the result of the patient's own approach to the disease and the support received from her surrounding structures. A sense of comfort is derived from the early diagnosis and associated omission of radiation therapy.

I am a positive person and was glad that the surgery was sufficient treatment. I did need to undergo further radiation or chemotherapy. I saw people being severely debilitated by further treatment. I do not easily complaint and was never depressed during the whole process of operation and recovery. I decided to be positive in the belief that negative thoughts would make things worse for me. When talking to people, you realize that there are several others around you who are diagnosed with cancer. I decided to take things on a day to day basis. Despite this, the cancer diagnosis came as a shock. I was lucky to be diagnosed early and did not need a radiation therapy. Participant 1

8.4 Discussion

The study provides evidence of the differences in the life experience of women with cervical cancer in the Western Cape to those of other South African women in Tshwane. Themes identified in the Tshwane studies identified ignorance, communication problems, delay in diagnosis and unmet expectations as major themes. The current study's themes were medical interaction, sexual impact, social impact and religious aspects.

8.4.1 Bronfenbrenner's ecological system model

Data analysis was completed and conceptualised within the context of Bronfenbrenner's Ecological System's Theory (Human Ecology Theory).⁽²⁸⁾ This theoretical framework is used to explain the experiences of women with cervical cancer. This theory describes human development regarding five systems: micro-, meso-, exo-, macro- and chrono-system. This framework is chosen because the experiences of the women in this study will be looked at both as an individual, for example, friends and families, as well as at a contextual level. The first level in this theory is the micro-system and is the person's immediate environment where she finds herself, where intimate and direct interactions occur, such as with friends, family, neighbours and work colleagues. The next level is the meso-system, which refers to the interactions or links between the micro-systems, where the individual actively participates. Per Bronfenbrenner, this would be, for example, the interactions taking place between the women's families and their partners/spouses. The next level is the exo-system, which includes those structures (from both micro- and meso-systems) that the individual is not directly implicated in, for example, the woman's spouse's/partner's working environment. The macro-level follows, which encompasses culture, values, laws and policy-making.⁽²⁸⁾ The last level is the chrono-system, which includes the shifts and transitions in one's lifespan. One example of this would be how a divorce, as an important life transition, may affect the women with cervical cancer's life. Bronfenbrenner's system allowed for the definition of women's experience at the different levels of function with her immediate (microsystem) and interaction with her further extended environment (macro-and exosystem). These levels, being interrelated, interact in the rendition of the individual woman's experiences. A clear example of a macro factor is the cultural differences as seen in the results of the current study with previously reported South African studies.

8.4.1.1 Microsystem.

The diagnosis of cervical cancer had an impact on the women's individual level by the threat of death posed by the disease. Their reactions of denial and disbelief result in self-recrimination due to the absence of routine gynaecological examinations and the ignorance of persistent symptoms. The women's reactions question the safety of the medical system as cancer was diagnosed, despite regular check-ups. Subsequent to the diagnosis, the treatment resulted in loss of reproductive capability and changed body image with a resultant fear of rejection by their partners.

8.4.1.2 Mesosystem and Exosystem.

The interaction with partner /husband, family and friends served as an important support structure and enabled the women to cope with the disease. Practical examples, for instance, transport to treatment facilities was important to women. In certain instances, this also lead to an increase in stress due to concerns of being a burden to the family. The presence or absence of a family history of cancer was expressed as a concern by women. The relationship, with specific emphasis on sexual and reproductive function, contributed to stress.

8.4.1.3 Macrosystem

Religious convictions of the women and their friends featured-as a support system to cope with the disease. One woman indicated that she is not religious but regarded her friend's willingness to pray for her as comforting.

8.4.2 The Kübler-Ross as a reference point for analysis of defence mechanisms and coping strategies.
Stages of the Kübler-Ross model is clearly evident with denial as described by:

Yes, I still cannot believe I had cancer. I never had bladder problems and never had an infection in my female parts. I still have everything that should be there. I never had a bladder infection like several of my friends had. You know the feeling of wet panties. Participant 3.

Denial, as described as a defence mechanism by Valliant, is defined as "avoiding the awareness of some painful aspect of reality". The painful diagnosis of cancer illicit a response of disbelief

with instinctually a degree of rationalization (regarding “several friends”). The patient thus consciously uses denial to respond but unconsciously utilises denial and rationalization as defences. The same woman using religion as a defence mechanism:

God was very very good to me. I prayed” God, please prove them wrong”. I prepared myself daily for treatment and did what they suggested. Yes, it is the power from above that I could carry on with treatment and my daily work as a baker. I feel this provided me certainty and served as my support. That is what I clung to. Participant 3

Religion becomes a defence mechanism but seamlessly morphs into a coping mechanism. This raises debate on the contention of Cramer’s differences between defence and coping (Table 1). The belief in God is a conscious process of coping but could be nonintentional as a pre-existing religious conviction. Albeit being used as a defence mechanism, the response is not associated with psychopathology as Cramer relates defence with pathology. Religion is thus a normality serving as a defence and a coping mechanism.

Anger in the Kübler-Ross model can be seen in self-reproach:

So anyway, so I just left it and then a year ago, I got a message duh, duh, duh your loop, it’s time for it and I thought yes, yes, yes, okay I’ll get there, I’ll get there, I’ll get there kind of thing, and then probably last year, yes last year it started. You know what I mean, I was obviously bleeding quite a bit and whatever, and I thought okay, now this is the loop, I need to go. But of course, I left it, and it got to a point, because I was still with my fiancée then at the time, it got to a point where I wouldn’t bleed constantly, but I’d be fine, and I wouldn’t be bleeding, but then obviously when we had sex, it would get really out of hand. And he kept on saying to me, you’ve got have this thing out, and I said yes, no, no, and it was a big issue, but anyway. So then eventually, because then we weren’t together anymore, so that was, you know what I mean. But I still knew I had to go because obviously...Participant 7

Anger can also be directed at health care providers:

No. I mean the chemo really wasn't that bad. The radiation, I don't think they prepare you enough for it. I mean they should literally tell you that it is going to be bad, literally. Well, I know they don't want to do that, but there must be a way that they can prepare you better for it. I mean they give you, I've still got it, they give you a little leaflet and they tell you this and that, but that, it's very broad and it's also not specific to you. Participant 7

Self-blame or blaming others may relate to the desire to identifying a cause for the current situation the patient finds herself in. The identified cause, be that self or externally inflicted, allows for reasoning to justify the situation and if preventable, can be appropriately addressed to prevent ongoing harm. The anger may lead to introspection and can be utilized as a defence, for instance, "I am in the situation because..." or as coping, for example, "I now know what caused the problem and will rectify matters". In the case of the irreversible disease of cervical cancer, the patient instituted life style changes are ineffective in changing the outcome. Anger is, therefore, a defence but if appropriately directed, serve as a coping mechanism. The duality of anger as both defence and coping mechanisms further illustrate the possible attempt at a distinction between the two mechanisms that should be viewed with caution.

A further stage in the Kübler Ross model is a negotiation.

I still said to her (my gynaecologist) Okay, so I'll just have a hysterectomy and we will be fine, you know. Because it was then they diagnosed it as Stage 2. So, I believe that Stage 2 is still within, it hasn't spread anywhere. So, it's not such well, to me, I thought it's not a big deal, it's over here, it's contained, it's not interfering in anything. Participant 7

This woman's experience illustrates an attempt to minimise the situation by stating "It's not a big deal." This is keeping with Cramer's description of defence mechanisms (manipulation) as an unconscious decision to minimize the reality of the threat and thus avoid suffering. The same participant utilizes the same mechanism later when she is confronted with radiation.

When I first went to the radiation doctor, I mean obviously, I'd read some things and they give you a whole lot of things to read and I think with cervical cancer, it's almost like you can't die from it. It's not, you know what I mean, it's not like breast cancer and some other cancers. And I think out of, this is my perception, I can't tell you others, but my perception is that out of all the cancers, this is the least life-threatening, because they can totally treat you and you can be fine as well. Participant 7

Based on the examples of defence and coping mechanisms, it clear that the two entities are intertwined. Defence mechanisms, as described by Valliant, could be a psychopathological process while coping mechanisms are a normal psychological response.⁽²³⁾ The fulcrum that balances defence and coping mechanism may be related to the personality involved. This adds a further dimension of possible distinction. Despite Lazarus' recognition in 1993 of the personality and situational aspects differentiating defence and coping mechanisms from each other little progress has been seen in the clinical benefit to patients with authors describing further research as "disappointing", "sterile" and "trivial".^(14,29,30) The progress in the theoretical distinction between defence and coping mechanism is further hampered by the responses that would be regarded as a normal reaction and in a psychopathological situation. At the core of the debate lies the importance of what implications the patient's experience, be that defence and/or coping, have on the support the environment provides. The environment includes the various levels, as described by Bronfenbrenner.⁽²⁸⁾ As the medical profession forms part of this matrix, it behoves healthcare providers dealing with women with cervical cancer to recognize the psychological response of their patients and this results in an appropriate support.

8.4.3 Limitations

Limitations of the current study include the distinct geographical and socioeconomic nature of the group that was studied. These results cannot be extrapolated to other populations. Due to the self-selection of candidates, a significant range of time after diagnosis occurred. This will

influence the results of a selective recall of events and reprioritising of goals take place with time. Utilising a different bereavement model to illustrate defence and coping mechanisms could influence the outcome. Objective assessment of the personality types of woman would enhance explanations to distinguish between defence and coping mechanisms.

8.5 Conclusion

The study describes the living experiences of women with cervical cancer in the private health sector in the Western Cape, as cultural and socioeconomic unique experiences. Kübler-Ross bereavement stages with the associated patient responses illustrate that a duality and dichotomy exist between defence and coping mechanisms.

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Chapter 9. Conclusions and recommendations

9 Introduction

The goal of medicine is not a delay of death, but an improvement in the QOL of patients. The clinical management of patients includes the disease-centred approach to biomedical diagnosis and treatment. Equally important is the patient-centred approach taking cognisance of, and caring for the human and humane aspects of the contextual experience of disease of an individual. This holistic approach to care is of relevance to women with cervical cancer in South Africa. The endemic incidence of advanced cervical cancer in South Africa results in a high mortality rate. These women have limited survival despite treatment. In this scenario of poor prognosis, the QOL of these women is important in the initial choice of treatment and the subsequent care. This dissertation describes the treatment-related changes in the QOL of women with cervical cancer in a developing country and its effect on the contextual factors of age, stage of disease, Human Immunodeficiency Virus status, treatment, level of education, income or employment status on their QOL.

9.1 Summary of research findings

9.1.1 Questionnaires

The ability to assess the QOL of these women requires quality-of-life questionnaires with proven psychometric properties of reliability, validity and acceptability. Of commensurate importance is that these questionnaires should be appropriate with regards to the language preferences of the women and should be culturally acceptable. The EORTC questionnaires comply with these criteria. For this dissertation, the EORTC CX24 questionnaire was translated and subsequently validated in Xhosa and Afrikaans. Specific attention was paid to the use of a colloquial vernacular of Afrikaans (“Afrikaaps”) spoken in the Western Cape Province. An analysis of the psychometric properties of these translated versions confirmed its clinical appropriateness. EORTC certification and recognition followed.

9.1.2 Medical and non-medical contextual factors influencing QOL of women with cervical

cancer Age at diagnosis influences women's priorities at a stage in their lives, as well as their QOL.

Women in the reproductive age prioritise future childbearing while menopausal women give preference to social relationships in their QOL. The literature review illustrates the interplay between age and the incidence of cervical cancer. As expected the stage and treatment of cervical cancer influenced QOL. Of importance is that no congruence is demonstrated between objective medical documentation and patient reported QOL.

The importance the QOL assessment of HIV-positive women with cervical cancer is discussed and the literature review identifies a lack of any prospective studies on the topic. The literature review of influence of the non-medical contextual factors on the QOL of women with cervical cancer identifies race and socioeconomic status as important. This is of relevance in South Africa as race serves as proxy to inadequate healthcare due to historical events and prevailing political dispensations.

9.1.3 Prospective evaluation of QOL of women with cervical cancer

The QOL of a woman with cervical cancer was evaluated in the context of the disease-related medical factors, e.g. stage of disease, treatment received and co-morbid disease. The most important co-morbid disease in women with cervical cancer is AIDS.

Equally important to the medical contextual factors are the patient-related factors, e.g. age, race, education level, employment status and income level. Women with cervical cancer treated at Tygerberg Hospital live in abject poverty with low educational levels, low employment rates and poor income. The dissertation identified advanced cervical cancer as a disease due to, and associated with, the disadvantaged socioeconomic status. Treatment improved the QOL of most women. The differential effect of radiation therapy versus chemo-radiation therapy to specific domains of QOL, e.g. pain, is documented. In the

absence of the survival benefit of chemo-radiation versus radiation in cases of advanced cervical cancer, judicious use of the latter is required.

9.1.4 HIV-positive women with cervical cancer

Invasive cervical cancer is an AIDS-defining disease and its co-occurrence in South Africa is high. AIDS poses challenges with regards to surgical treatment of cervical cancer. It increases toxicity associated with radiation therapy and chemo-radiation therapy and requires adaptation of treatment. This dissertation identified HIV-positive women with cervical cancer younger than their HIV-negative counterparts. The QOL of HIV-positive and HIV-negative women at diagnosis was similar. Global health improved significantly after treatment in HIV-negative women. A persistent decrease in the specific QOL domains in HIV-positive women could be related to AIDS-associated diseases. Peripheral neuropathy is associated with AIDS and its treatment. Cisplatin, used as chemotherapy during chemo-radiation, may cause and exacerbate existing neuropathy. Counter-intuitively peripheral neuropathy QOL initially improved after treatment for cervical cancer in HIV-positive women returning to pre-treatment levels thereafter. The judicious use of chemo-radiation therapy, without compromising QOL, is particularly important in HIV-positive women with cervical cancer.

9.1.5 Contextual QOL of cervical cancer survivors

In this dissertation, cervical cancer survivors are identified as postmenopausal women with poor socioeconomic status as reflected by an income under the prevailing poverty line. Their HIV status is nine percent versus the 22% HIV positive statuses of newly diagnosed cases of cervical cancer. This difference occurs due to more disease-related deaths in HIV-positive women. Advanced stage and unemployment decrease the QOL related to physical function. Married status increased sexual activity and decreased sexual worry. Positive HIV-status decreased emotional role function and decreased sexual function without decreasing sexual

activity.

9.1.6 Qualitative research and cervical cancer

Qualitative research methods are used in social science research. The literature review identifies the impact of the various aspects of cervical cancer on the lived experience of women by their narrative account. It represents a patient-centred approach to explore their unique situations and disease related impact on their lives. The original qualitative research in the dissertation identifies the lived experience as cultural specific. The narratives of the women illustrate their bereavement process in dealing with cervical cancer and its impact. Their responses reflect psychological mechanisms to defend themselves but also cope with their situation.

9.2 Discussion on aims, proposed scope of research and hypothesis

The initial aims, scope of research was formulated as follows:

9.2.1 Aims and proposed scope of research

The appropriateness of chemo radiation therapy versus radiation therapy as treatment for advanced cervical cancer in the absence of survival benefit raises questions with regard to the impact on the QOL of the two treatment modalities. The co-occurrence of HIV in women with cervical cancer has further impact on treatment and QOL.

The research aims to evaluate the contextual factors influencing the QOL of cervical cancer cases. The initial phase of the study identifies as the appropriate questionnaires to be used. The EORTC QLQ CX24 is identified and translated into the indigenous languages of isiXhosa and Afrikaans and psychometric evaluated. The contextual factors of age, race, educational level, employment status, income and marital status, stage of disease, treatment and HIV-status are included in the analysis as possible confounding variable influencing the QOL domains. These factors are studied in a prospective study on newly diagnosed women with cervical cancer and in a cross-sectional study on cervical cancer survivors. To reflect on the women's own

perspectives a qualitative study is performed to document the women's lived experience of cervical cancer.

9.2.2 Hypothesis

Null hypothesis: The contextual factors of age, race, educational level, employment status, income and marital status, stage of disease, treatment and HIV-status does not influence the QOL of cervical cancer cases. In view of the results of the research in the thesis the null hypothesis can be rejected and the alternative hypothesis accepted.

9.2.3 Discussion

The aim of the study to translate, validate and confirmation the psychometric properties of the isiXhosa and Afrikaans translated versions of EORTC QLQ CX24 was accomplished with official recognition by the EORTC QOL group (see addendum). Subsequently the translated questionnaire and the EORTC QLQ C30 questionnaires were utilised in a prospective study on newly diagnosed women with cervical cancer and further a cross-sectional study on cervical cancer survivors to assess the influence of the medical and non-medical contextual factors on their QOL. These studies proofed a significant influence of the contextual factors on the women's QOL. The dissertation contributes to new knowledge in the following aspects: Validated and psychometrically assessed isiXhosa and Afrikaans translated version of EORTC QLQ CX 24 were produced. The contextual factors influencing the QOL of women in a resourced constrained environment, with predominantly advanced cervical cancer were analysed and described. A particular contribution, previously undescribed, was the influence of HIV status on the QOL.

9.3 Conclusions and recommendations

Objective QOL assessment of women with cervical cancer allows for identification of medical and contextual factors influencing the various QOL domains. It allows for tailoring

future treatment protocols in treatment of the various stages of the disease to obviate a decrease in QOL. Equally important is the patient's experience obtained by qualitative research. Qualitative research contributes a patient-centred narrative of their lived experience of cervical cancer and this is as important as the results of quantitative research. The two research methods are neither mutually exclusive nor interchangeable but represent a continuum of the process of evaluating QOL. The interdependence of qualitative and quantitative research methods is an example of transdisciplinary cooperation between social sciences e.g. psychology, generating patient-centred narratives of the lived experience of cancer by qualitative research. Themes identified by qualitative research form the basis for the domains to be assessed by quantitative questionnaires formulated by natural sciences e.g. medicine.

Transdisciplinary research is defined as research efforts conducted by investigators from different disciplines working jointly to create new conceptual, theoretical, methodological, and translational innovations that integrate and move beyond discipline-specific approaches to address a common problem. The EORTC guidelines in developing new questionnaire processes consist of four phases: generation of relevant QOL issues; conversion of the QOL issues into a set of items; pre-testing the item list or preliminary module questionnaire; and large-scale international field-testing.

The generation of relevant QOL issues is done by interviews with patients and multiple disciplines of healthcare providers (1). This is done by qualitative research methods. In considering the information gathered from interviews, the responses of patients should be given highest priority. QOL measures must be derived in a patient-centred way, to ensure greatest content validity. The initial role of qualitative research is pivotal to the further development of the questionnaire. Subsequent questionnaire development by natural sciences involves validation followed by analysis of psychometric analysis.

A recent example of the cooperative role of qualitative and quantitative research is illustrated by the development of the Quality of Working Life Questionnaire for Cancer Survivors (QWLQ-CS). The Dutch research group initially conducted a systematic literature review to identify issues that contribute to the quality of working life (QWL) of employees with a chronic physical condition (2). Secondly, the Dutch group generated and selected QWL issues for cancer survivors in a qualitative study.

The Dutch group held focus-group discussions with cancer survivors and oncological occupational physicians and interviewed employers. In the final step, they combined the QWL issues from the systematic literature review with the issues generated in the qualitative study to formulate a questionnaire that was subsequently used (3). Quantitative and qualitative is thus interdependent and is complimentary in research and confirm the need for transdisciplinary cooperation in the formulation of QOL questionnaires.

The relation between qualitative and quantitative methods to determine women's QOL should not be limited to research but should be extended to clinical care. Healthcare providers should avail themselves of the value of qualitative input by their patients during their journey with cervical cancer. The objective quantitative assessment plays an important role in deciding on treatment modalities and their impact on QOL. Qualitative and quantitative approaches should be part of every healthcare worker's acumen taking care of women with cervical cancer. In biomedical science, the laboratory bench translation research benefits the patient by its eventual bedside application. In QOL science the transition of research to the benefit of the patient relies on health workers recognising the QOL-related needs of their patients in a quantitative determination but equally important a qualitative fashion.

9.3 Recommendations

1. QOL should be one of the primary clinical outcomes of the management of women with cervical cancer. In clinical practice, utilizing questionnaires allows for objective assessment of QOL and the impact of treatment on it. Contextual factors influencing QOL should be recognized and considered in deciding on therapy.
2. Chemo-radiation therapy should be offered judiciously in cases of advanced disease due to the limited enhanced QOL in comparison to radiation therapy.
3. HIV status significantly affects treatment of women with cervical cancer. Despite this, the judicious use of chemo-radiation may improve QOL and should be considered in the care of HIV-positive women with cervical cancer.
4. Healthcare providers dealing with women with cervical cancer should be familiar with the psychological reactions of patients to their disease and its treatment. Appropriate support should be provided.
5. State of the art management of women with cervical cancer requires a multidisciplinary team approach to consider all treatment options and develop an individual treatment plan for each case to reduce mortality and improve the QOL for the woman. Competence in the qualitative and quantitative assessment of the patient's QOL should be part of this team.
6. Future research should be directed at including QOL assessment when introducing new treatment regimens especially in resourced constrained environments. In the absence of survival benefits, the aim of introducing new treatment regimens should focus on the impact on QOL.
7. Advanced cervical cancer will remain a major burden of disease in South Africa for the near future. The impact of the disease on an individual woman's survival and QOL remains of tantamount importance. Concurrently the disease impacts on the broader community with financial implications for health care systems. Future research on the quality-adjusted life

year or quality-adjusted-life-year (QALY) would provide an economic evaluation of disease burden, its treatment and the quality and quantity of life lived after diagnosis of cervical cancer.

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Dagmara Kuliś
Translation Team Leader
Quality of Life Department
Direct Phone: + 32 02 774 16.80
QLDpt Fax: + 32 02 779.45.68
dagmara.kulis@eortc.be

Brussels, 8th May 2012

CONFIRMATION

Hereby we confirm that the **EORTC QLQ-CX24** questionnaire translated into **Xhosa** has been approved by the EORTC Quality of Life Department as a finalised translation performed in accordance with the EORTC Translation Manual.

Signed by:

Dagmara Kuliś
Translation Team Leader
for EORTC Quality of Life Group



Dagmara Kuliś Translation

Team Leader

QOL Department

Direct Phone: + 32 02 774 16.80

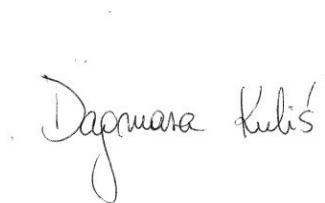
QLDpt Fax: + 32 02 779.45.68

dagmara.kulis@eortc.be

Brussels, 21st March 2017

CONFIRMATION

Hereby we confirm that the **EORTC QLQ-CX24** questionnaire translated into **Afrikaans** has been approved by the EORTC QOL Department as a finalised translation performed in accordance with the EORTC Translation Procedure.



Signed by: *Dagmara Kuliś*

Translation Team Leader, EORTC Headquarters, Brussels